Electronic Supplementary Information

Synthesis and biological evaluation of conformationally restricted adenine bicycloribonucleosides

Hubert Hřebabecký,[a] Eliška Procházková,[a] Michal Šála,[a] Pavla Plačková,[a] Eva Tloušťová,[a] Ona Barauskas,[b] Yu-Jen Lee,[b] Yang Tian,[b] Richard Mackman[b] and Radim Nencka[a,*]

Contents

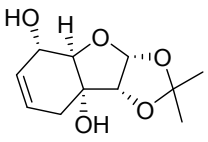
1. Yields, physical, analytical, and spectral data S1-S9

2. In situ structure determination of intermediate **20b** (supplementary figures) S10-S11

3. ^{1}H NMR, ^{13}C NMR, ^{31}P NMR for the new compounds S12-S46

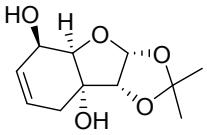
Yields, physical, analytical, and spectral data

(3a*R*,4a*R*,5*S*,8a*R*,8b*R*)-2,2-Dimethyl-3a,4a,5,8,8a,8b-hexahydro-[1,3]dioxolo[4,5-*b*]benzofuran-5,8a-diol (4a)



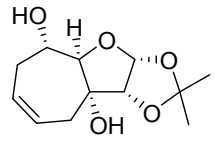
Yield 2.206 g (32% based on **1**) of a greyish solid foam. $[\alpha]_D^{20}$ +14.7 (c = 0.443, $CHCl_3$). Found: C, 57.86; H, 7.10. Calc. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.26 (s, 3 H, CH_3exo), 1.47 (s, 3 H, CH_3endo), 1.84 (m, 1 H, H-8eq), 1.97 (m, 1 H, H-8ax), 3.96 (d, $J_{4a\text{-}5}$ = 4.2, 1 H, H-4a), 4.14 (m, 1 H, H-5), 4.17 (d, $J_{8b\text{-}3a}$ = 3.6, 1 H, H-8b), 4.79 (bs, 1 H, 5-OH), 5.04 (bs, 1 H, 8a-OH), 5.46–5.48 (m, 2 H, H-6, H-7), 5.68 (d, $J_{3a\text{-}8b}$ = 3.6, 1 H, H-3a). ^{13}C NMR (125 MHz, d6-DMSO): δ 26.51 (CH_3exo), 26.55 (CH_3endo), 32.94 (C-8), 64.08 (C-5), 76.02 (C-4a), 76.09 (C-8a), 83.54 (C-8b), 103.56 (C-3a), 111.69 (C-2), 123.55 (C-7), 128.50 (C-6). HRMS (ESI): calcd. for $C_{11}H_{16}O_5Na$ [M + Na] 251.08899; found: 251.08894.

(3a*R*,4a*R*,5*R*,8a*R*,8b*R*)-2,2-Dimethyl-3a,4a,5,8,8a,8b-hexahydro-[1,3]dioxolo[4,5-b]benzofuran-5,8a-diol (4b)



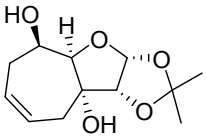
Yield 1.17 g (18% based on **1**) of a greyish crystals. M.p. 94-97 °C (diethyl ether). $[\alpha]_D^{20}$ +117 (c = 0.378, $CHCl_3$). Found: C, 57.86; H, 6.94. Calc. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.26 (s, 3 H, CH_3exo), 1.47 (s, 3 H, CH_3endo), 1.76 (dm, J_{gem} = 18.0, 1 H, H-8eq), 2.04 (ddm, J_{gem} = 18.0, J_{8ax-7} = 5.7, 1 H, H-8ax), 3.81–3.91 (m, 2 H, H-4a, H-5), 4.11 (d, J_{8b-3a} = 3.8, 1 H, H-8b), 4.69 (s, 1 H, 8a-OH), 4.82 (d, J_{OH-5} = 5.9, 1 H, 5-OH), 5.62 (d, J_{3a-8b} = 3.8, 1 H, H-3a), 5.65 (m, 1 H, H-7), 5.69 (m, 1 H, H-6). ^{13}C NMR (125 MHz, d6-DMSO): δ 26.54 (CH_3exo), 26.68 (CH_3endo), 31.33 (C-8), 63.70 (C-5), 72.83 (C-8a), 80.34 (C-4a), 83.55 (C-8b), 103.11 (C-3a), 111.51 (C-2), 124.09 (C-7), 127.76 (C-6). ESI MS, *m/z* (%): 252.1 (15) [M + Na + H], 251.1 (100) [M + Na]. HRMS (ESI): calcd. for $C_{11}H_{16}O_5Na$ [M + Na] 251.08899; found: 251.08895.

(3a*R*,4a*R*,5*S*,9a*R*,9b*R*)-2,2-Dimethyl-4a,5,6,9,9a,9b-hexahydro-3a*H*-cyclohepta[4,5]furo[2,3-d][1,3]dioxole-5,9a-diol (7a)



Yield 1.73 g (26% based on **1**) of a white crystals. M.p. 135.5-136.5 °C (diethyl ether). $[\alpha]_D^{20}$ +39.1 (c = 0.399, $CHCl_3$). Found: C, 59.47; H, 7.47. Calc. for $C_{25}H_{24}O_7$: C, 59.24; H, 7.49%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.26 (s, 3 H, CH_3 exo), 1.47 (s, 3 H, CH_3 endo), 1.91 (ddm, J_{gem} = 16.4, J_{6eq-7} = 8.2, J_{6eq-5} = 1.2, 1 H, H-6eq), 2.03 (ddm, J_{gem} = 17.4, J_{9ax-8} = 7.3, 1 H, H-9ax), 2.19 (dm, J_{gem} = 17.4, H-9eq), 2.45 (m, 1 H, H-6ax), 3.51 (m, 1 H, H-5), 3.68 (dd, J_{4a-5} = 7.1, J_{4a-9en} = 1.7, 1 H, H-4a), 3.98 (d, J_{9b-3a} = 3.8, 1 H, H-9b), 4.64 (m, 1 H, 9a-OH), 4.95 (d, J_{OH-5} = 4.8, 1 H, 5-OH), 5.32 (m, 1H, H-8), 5.60 (m, 1 H, H-7), 5.70 (d, J_{3a-9b} = 3.8, 1 H, H-3a). ^{13}C NMR (125 MHz, d6-DMSO): δ 26.78 (CH_3 exo), 26.98 (CH_3 endo), 33.17 (C-6), 33.71 (C-9), 72.07 (C-5), 77.43 (C-9a), 85.58 (C-9b, 86.79 (C-4a), 102.92 (C-3a), 111.13 (C-2), 125.18 (C-8), 127.85 (C-7). HRMS (ESI): calcd. for $C_{12}H_{18}O_5Na$ [M + Na] 265.10464; found: 265.10462.

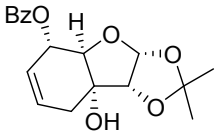
(3aR,4aR,5R,9aR,9bR)-2,2-Dimethyl-4a,5,6,9,9a,9b-hexahydro-3aH-cyclohepta[4,5]furo[2,3-d][1,3]dioxole-5,9a-diol (7b)



Yield 2.06 g (30% based on **1**) of a white crystals. M.p. 79–80 °C (diethyl ether). $[\alpha]_D^{20}$ -5.1 (c = 0.454, $CHCl_3$). Found: C, 59.61; H, 7.57. Calc. for $C_{25}H_{24}O_7$: C, 59.24; H, 7.49%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.26 (s, 3 H, CH_3 exo), 1.46 (s, 3 H, CH_3 endo), 1.91 (ddm, J_{gem} = 14.4, J_{6eq-7} = 8.0, 1 H, H-6eq), 1.95 (ddd, J_{gem} = 14.4, J_{9ax-8} = 8.0, J_{9ax-4a} = 0.9, 1 H, H-9ax), 2.19 (dm, J_{gem} = 14.4, 1 H, H-9eq), 2.56 (m, 1 H, H-6ax), 3.57 (m, 1 H, H-5), 3.99 (d, J_{9b-3a} = 3.8, 1 H, H-9b), 4.00 (m, 1 H, H-4a), 4.71 (d, J_{OH-5} = 5.8, 1 H, 5-OH), 4.83 (t, J_{OH-9b} = J_{OH-9eq} = 0.7, 1 H, 9a-OH), 5.53 (m, 1 H, H-8), 5.71 (d, J_{3a-9b} = 3.8, 1 H, H-3a), 5.74 (m, 1 H, H-7). ^{13}C NMR (125 MHz, d6-DMSO): δ 26.66 and 26.73 (CH_3), 30.09 (C-6), 32.02 (C-9), 65.40 (C-5), 78.06 (C-9a), 83.20 (C-4a), 84.38 (C-9b), 102.95 (C-3a),

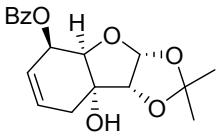
111.35 (C-2), 127.50 (C-8), 129.60 (C-7). ESI MS, *m/z* (%): 266.3 (14) [M + Na + H], 265.3 (100) [M + Na]. HRMS (ESI): calcd. for $C_{12}H_{18}O_5Na$ [M + Na] 265.10464; found: 265.10461.

(3a*R*,4a*R*,5*S*,8a*R*,8b*R*)-8a-Hydroxy-2,2-dimethyl-3a,4a,5,8,8a,8b-hexahydro-[1,3]dioxolo[4,5-b]benzofuran-5-yl benzoate (5a)



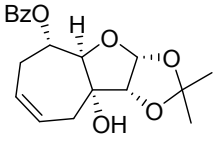
Yield 1.53 g (92%) of a white crystals. M.p. 104-106 °C. $[\alpha]_D^{20}$ +209.8 (c = 0.324, $CHCl_3$). Found: C, 65.16; H, 6.25. Calc. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.28 (s, 3 H, CH_3exo), 1.46 (s, 3 H, H-CH_3endo), 1.93 (dm, J_{gem} = 18.6, 1 H, H-8eq), 2.21 (dd, J_{gem} = 18.6, $J_{8ax\text{-}7}$ = 5.6, 1 H, H-8ax), 4.06 (m, 1 H, H-4a), 4.21 (d, $J_{8b\text{-}3a}$ = 3.6, 1 H, H-8b), 5.15 (s, 1 H, 8a-OH), 5.32 (m, 1 H, H-5), 5.71 (d, $J_{3a\text{-}8b}$ = 3.6, 1 H, H-3a), 5.79 (dm, $J_{6\text{-}7}$ = 10.2, 1 H, H-6), 5.96 (m, 1 H, H-7), 7.52 (m, 2 H, H-3′, H-5′), 7.66 (tm, $J_{4'\text{-}3'} = J_{4'\text{-}5'}$ = 7.4, 1 H, H-4′), 8.00 (m, 2 H, H-2′, H-6′). ^{13}C NMR (125 MHz, d6-DMSO): δ 26.41 (CH_3endo), 26.73 (CH_3exo), 31.41 (C-8), 66.11 (C-5), 72.57 (C-8a), 76.64 (C-4a), 85.53 (C-8b), 103.44 (C-3a), 111.93 (C-2), 121.75 (C-6), 128.80 (C-3′, C-5′), 128.97 (C-7), 129.73 (C-2′, C-6′), 129.92 (C-1′), 133.59 (C-4′), 165.26 (C=O). ESI MS, *m/z* (%): 356.1 (22) [M + Na + H], 355.1 (100) [M + Na]. HRMS (ESI): calcd. for $C_{18}H_{20}O_6Na$ [M + Na] 355.11521; found: 355.11516.

(3a*R*,4a*R*,5*R*,8a*R*,8b*R*)-8a-Hydroxy-2,2-dimethyl-3a,4a,5,8,8a,8b-hexahydro-[1,3]dioxolo[4,5-b]benzofuran-5-yl benzoate (5b)



Yield 1.56 g (94%) of a white crystals. M.p. 120.5–121.5 °C. $[\alpha]_D^{20}$ -50.9 (c = 0.456, $CHCl_3$). Found: C, 64.91; H, 5.90. Calc. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.26 (s, 3 H, CH_3exo), 1.44 (s, 3 H, CH_3endo), 2.00 (m, 1 H, H-8eq), 2.13 (m, 1 H, H-8ax), 4.25 (d, $J_{8b\text{-}3a}$ = 3.5, 1 H, H-8b), 4.28 (dd, $J_{4a\text{-}5}$ = 4.5, $J_{4a\text{-}8ax}$ = 1.7, 1 H, H-4a), 5.40 (s, 1 H, 8a-OH), 5.59–5.64 (m, 2 H, H-5, H-6), 5.76 (d, $J_{3a\text{-}8b}$ = 3.5, 1 H, H-3a), 5.77 (m, 1 H, H-7), 7.55 (m, 2 H, H-3′, H-5′), 7.68 (m, 1 H, H-4′), 7.97 (m, 2 H, H-2′, H-6′). ^{13}C NMR (125 MHz, d6-DMSO): δ 26.46 (CMe_2exo), 26.56 (CMe_2endo), 32.67 (C-8), 68.78 (C-5), 73.08 (C-4a), 76.42 (C-8a), 83.23 (C-8b), 103.87 (C-3a), 112.01 (C-2), 122.86 (C-6), 127.10 (C-7), 129.02 (C-3′, C-5′), 129.51 (C-2′, C-6′), 129.76 (C-1′), 133.74 (C-4′), 165.44 (C=O). ESI MS, *m/z* (%): 356.0 (20) [M + Na + H], 355.0 (100) [M + Na]. HRMS (ESI): calcd. for $C_{18}H_{20}O_6Na$ [M + Na] 355.11521; found: 355.11520.

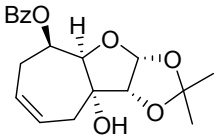
(3a*R*,4a*R*,5*S*,9a*R*,9b*R*)-9a-Hydroxy-2,2-dimethyl-4a,5,6,9,9a,9b-hexahydro-3a*H*-cyclohepta[4,5]furo[2,3-d][1,3]dioxol-5-yl benzoate (8a)



Yield 1.54 g (89%) of a white crystals. M.p. 169-170 °C. $[\alpha]_D^{20}$ -7.3 (c = 0.259, $CHCl_3$). Found: C, 65.80; H, 6.50. Calc. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.27 (s, 3 H, CH_3exo), 1.53 (s, 3 H, CH_3endo), 2.12 (ddd, J_{gem} = 16.0, $J_{6eq\text{-}7}$ = 8.2, $J_{6eq\text{-}5}$ = 1.5, 1 H, H-6eq), 2.18 (ddm, J_{gem} = 17.6, $J_{9ax\text{-}8}$ = 7.4, 1 H, H-9ax), 2.35 (dm, J_{gem} = 17.6, 1 H, H-9eq), 2.66 (m, 1 H, H-6ax), 4.08 (d,

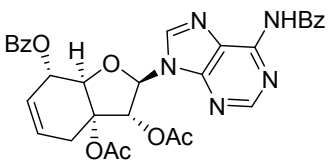
$J_{9b\text{-}3a}$ = 3.7, 1 H, H-9b), 4.15 (dd, $J_{4a\text{-}5}$ = 7.6, $J_{4a\text{-}9ax}$ = 1.4, 1 H, H-4a), 5.04 (s, 1 H, 9a-OH), 5.05 (ddd, $J_{5\text{-}6ax}$ = 11.6, $J_{5\text{-}6eq}$ = 1.5, $J_{5\text{-}4a}$ = 7.6, 1 H, H-5), 5.49 (m, 1 H, H-8), 5.68 (m, 1 H, H-7), 5.74 (d, $J_{3a\text{-}9b}$ = 3.7, 1 H, H-3a), 7.54 (m, 2 H, H-3′, H-5′), 7.67 (m, 1 H, H-4′), 7.95 (m, 2 H, H-2′, H-6′). ^{13}C NMR (125 MHz, d6-DMSO): δ 26.71 (CH_3exo), 27.09 (CH_3endo), 29.34 (C-6), 33.45 (C-9), 75.63 (C-5), 77.69 (C-9a), 82.98 (C-4a), 85.43 (C-9b), 103.09 (C-3a), 111.56 (C-2), 126.22 (C-8), 126.31 (C-7), 129.01 (C-3′, C-5′), 129.36 (C-2′, C-6′), 129.94 (C-1′), 133.64 (C-4′), 165.05 (C=O). ESI MS, *m/z* (%): 370.1 (22) [M + Na + H], 369.1 (100) [M + Na]. HRMS (ESI): calcd. for $C_{19}H_{22}O_6Na$ [M + Na] 369.13086; found: 36913090.

(3a*R*,4a*R*,5*R*,9a*R*,9b*R*)-9a-Hydroxy-2,2-dimethyl-4a,5,6,9,9a,9b-hexahydro-3a*H*-cyclohepta[4,5]furo[2,3-d][1,3]dioxol-5-yl benzoate (8b)



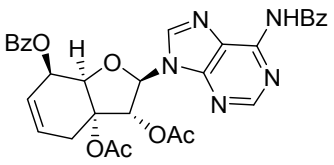
Yield 1.28 g (74%) of a white crystals. M.p. 97.5-99.5 °C. $[\alpha]_D^{20}$ -17.6 (c = 0.33, $CHCl_3$). Found: C, 65.73; H, 6.36. Calc. for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40%. ^{1}H NMR (500 MHz, d6-DMSO): δ 2.08-2.14 (m, 2 H, H-6B, H-10B), 2.33 (dm, J_{gem} = 1.0, 1 H, H-9A), 2.81 (m, 1 H, H-6A), 4.09 (d, $J_{9b\text{-}3a}$ = 3.7, 1 H, H-9b), 4.17 (m, 1 H, 4a), 5.08 (dt, $J_{5\text{-}6A}$ = 11.2, $J_{5\text{-}6B}$ = $J_{5\text{-}4a}$ = 2.4, 1 H, H-5), 5.15 (s, 1 H, 9a-OH), 5.69 (m, 1 H, H-8), 5.81 (d, $J_{3a\text{-}9b}$ =3.7, 1 H, H-3a), 5.84 (m, 1 H, H-7), 7.54 (m, 2 H, H-3′, H-5′), 7.67 (m, 1 H, H-4′), 7.93 (m, 2 H, H-2′, H-6′). ^{13}C NMR (125 MHz, d6-DMSO): δ 26.68 (C-6), 26.62 and 26.82 (2 × CH_3), 32.03 (C-9), 69.63 (C-5), 78.57 (C-9a), 80.59 (C-4a), 84.13 (C-9b), 103.25 (C-3a), 111.71 (C-2), 127.99 (C-7), 128.85 (C-8), 129.01 (C-3′, C-5′), 129.34 (C-2′, C-6′), 130.05 (C-1′), 133.63 (C-4′), 165.13 (COO). ESI MS, *m/z* (%): 370.1 (21) [M + Na + H], 369.1 (100) [M + Na]. HRMS (ESI): calcd. for $C_{19}H_{22}O_6Na$ [M + Na] 369.13086; found: 369.13078.

(2*R*,3*R*,3a*R*,7*S*,7a*R*)-2-(6-Benzamido-9*H*-purin-9-yl)-7-(benzoyloxy)-2,3,3a,4,7,7a-hexahydrobenzofuran-3,3a-diyl diacetate (9a)



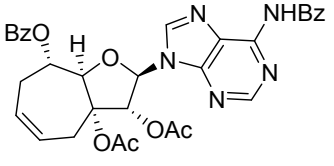
Yield 1.39 g (58%) of a white solid foam. $[\alpha]_D^{20}$ +87.0 (c = 0.300, $CHCl_3$). Found: C, 61.98; H, 4.60; N, 11.37. Calc. for $C_{31}H_{27}N_5O_8$: C, 62.31; H, 4.55; N, 11.72%. ^{1}H NMR (500 MHz, d6-DMSO): δ 2.18 (s, 3 H, 3a-$OCOCH_3$), 2.04 (s, 3 H, 3-$OCOCH_3$), 3.07 (m, 2 H, H-4), 4.75 (d, $J_{7a\text{-}7}$ = 4.2, 1 H, H-7a), 5.93 (m, 1 H, H-6), 6.05 (m, 1 H, H-7), 6.06 (m, 1 H, H-5), 6.31 (d, $J_{3\text{-}2}$ = 6.3, 1 H, H-3), 6.41 (d, $J_{2\text{-}3}$ = 6.3, 1 H, H-2), 7.53 (m, 2 H, m-benzoyl), 7.55 (m, 2 H, m-benzoylamino), 7.65 (m, 1 H, p-benzoylamino), 7.67 (m, 1 H, p-benzoyl), 7.98 (m, 2 H, o-benzoyl), 8.05 (m, 2 H, o-benzoylamino), 8.76 (s, 1 H, H-8′), 8.80 (s, 1 H, H-2′), 11.28 (bs, 1 H, NH). ^{13}C NMR (125 MHz, d6-DMSO): δ 20.55 (3-OCO**C**H_3), 21.67 (3a-OCO**C**H_3), 30.12 (C-4), 70.96 (C-7), 74.91 C-3), 80.83 (C-7a), 81.51 (C-3a), 86.09 (C-2), 124.23 (C-6), 126.18 (C-5′), 128.05 (C-5), 128.69, 128.72 (o-, m-benzoylamino), 129.02 (m-benzoyl), 129.46 (i-benzoyl), 129.53 (o-benzoyl), 132.73 (p-benzoylamino), 133.46 (i-benzoylamino), 133.85 (p-benzoyl), 144.35 (C-8′), 150.90 (C-6′), 151.98 (C-2′), 152.13 (C-4′), 165.18 (COO), 165.85 (CONH), 169.74 (3-$OCOCH_3$), 170.04 (3a-$OCOCH_3$). ESI MS, *m/z* (%): 621.2 (36) [M + Na + H], 620.2 (100) [M + Na], 598.2 (24) [M + H]. HRMS (ESI): calcd. for $C_{31}H_{28}O_8N_5$ [M + H] 598.19324; found: 598.19326.

(2*R*,3*R*,3a*R*,7*R*,7a*R*)-2-(6-Benzamido-9*H*-purin-9-yl)-7-(benzoyloxy)-2,3,3a,4,7,7a-hexahydrobenzofuran-3,3a-diyl diacetate (9b)



Yield 1.41 g (55%) of a white solid foam. $[\alpha]_D^{20}$ -23.2 (c = 0.263, $CHCl_3$). Found: C, 61.66; H, 4.70; N, 10.89. Calc. for $C_{31}H_{27}N_5O_8 \cdot 0.5\ CH_3COOC_2H_5$: C, 61.77; H, 4.87; N, 10.91%. ^{1}H NMR (500 MHz, d6-DMSO): δ 2.06 (s, 3 H, 3-OCOCH_3), 2.18 (s, 3 H, 3a-OCOCH_3), 2.78 (dm, J_{gem} = 18.0, 1 H, H-4B), 3.26 (ddm, J_{gem} = 18.0, J_{4A-5} = 4.7, 1 H, H-4A), 4.86 (dd, J_{7a-7} = 4.3, J_{7a-2} = 0.8, 1 H, H-7a), 5.83 (m, 1 H, H-7), 5.97 (m, 1 H, H-6), 5.99 (d, J_{3-2} = 5.7, 1 H, H-3), 6.03 (m, 1 H, H-5), 6.32 (d, J_{2-3} = 5.7, 1 H, H-2), 7.50 (m, 2 H, m-benzoyl), 7.55 (m, 2 H, m-benzoylamino), 7.63-7.67 (m, 2 H, p-benzoyl, p-benzoylamino), 7.94 (m, 2 H, o-benzoyl), 8.04 (m, 2 H, o-benzoylamino), 8.54 (s, 1 H, H-8′), 8.75 (s, 1 H, H-2′), 11.27 (bs, 1 H, NH). ^{13}C NMR (125 MHz, d6-DMSO): δ 20.54 (3-OCO**C**H_3), 21.45 (3a-OCO**C**H_3), 30.59 (C-4), 68.78 (C-7), 76.65 (C-3), 78.74 (C-7a), 80.61 (C-3a), 85.85 (C-2), 125.75 (C-5′), 126.00 (C-6), 126.61 (C-5), 128.69, 128.71 (o-, m-benzoylamino), 129.02 (m-benzoyl), 129.35 (i-benzoyl), 129.54 (o-benzoyl), 132.73 (p-benzoylamino), 133.41 (i-benzoylamino), 133.86 (p-benzoyl), 143.23 (C-8′), 150.89 (C-6′), 152.18 (C-2′), 152.23 (C-4′), 164.38 (COO), 165.82 (CONH), 169.69 (3-OCOCH_3), 169.88 (3a-OCOCH_3). ESI MS, *m/z* (%): 621.1 (34) [M + Na + H], 620.1 (100) [M + Na], 598.1 (30) [M + H]. HRMS (ESI): calcd. for $C_{31}H_{28}O_8N_5$ [M + H] 598.19324; found: 598.19337.

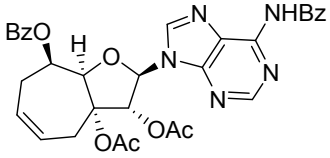
(2*R*,3*R*,3a*R*,8*S*,8a*R*)-2-(6-Benzamido-9H-purin-9-yl)-8-(benzoyloxy)-3,3a,4,7,8,8a-hexahydro-2H-cyclohepta[b]furan-3,3a-diyl diacetate (12a)



Yield 1.65 g (63%) of a white solid foam. $[\alpha]_D^{20}$ +41.8 (c = 0.385, $CHCl_3$). Found: C, 62.32; H, 5.00; N, 10.82. Calc. for $C_{32}H_{29}N_5O_8 \cdot 0.5\ CH_3COOC_2H_5$: C, 62.28; H, 5.07; N, 10.68%. ^{1}H NMR (500 MHz, d6-DMSO): δ 2.03 (s, 3 H, 3-OCOCH_3), 2.12 (s, 3 H, 3a-OCOCH_3), 2.54 (dm, J_{gem} = 16.4, 1 H, H-7B), 2.71 (m, 1 H, H-7A), 3.21 (dm, J_{gem} = 17.3, 1 H, H-4B), 3.36 (m, 1 H, H-4A), 4.62 (dd, J_{8a-2} = 1.3, J_{8a-8} = 7.9, 1 H, H-8a), 5.47 (ddd, J_{8-7A} = 11.0, J_{8-7B} = 2.4, J_{8-8a} = 7.9, 1 H, H-8), 5.58 (m, 1 H, H-5), 5.80 (m, 1 H, H-6), 6.02 (d, J_{3-2} = 5.1, 1 H, H-2), 6.26 (d, J_{2-3} = 5.1, 1 H, H-2), 7.52 (m, 2 H, m-benzoyl), 7.55 (m, 2 H, m-benzoylamino), 7.63-7.68 (m, 2 H, p-benzoylamino, p-benzoyl), 7.97 (m, 2 H, o-benzoyl), 8.04 (m, 2 H, o-benzoylamino), 8.68 (s, 1 H, H-8′), 8.79 (s, 1 H, H-2′), 11.28 (bs, 1 H, NH). ^{13}C NMR (125 MHz, d6-DMSO): δ 83.93 (C-8a), 20.51 (3-OCO**C**H_3), 21.15 (3a-OCO**C**H_3), 30.48 (C-7), 31.89 (C-4), 72.65 (C-8), 75.96 (C-3), 82.85 (C-3a), 87.17 (C-2), 124.37 (C-5), 125.93 (C-5′), 127.70 (C-6), 128.71, 128.61 (o-, m-benzoyl), 128.96 (m-benzoyl), 129.52 (o-benzoyl), 129.57 (i-benzoyl), 132.70 (p-benzoylamino), 133.48 (i-benzoylamino), 133.80 (p-benzoyl), 143.95 (C-8′), 150.91 (C-6′), 152.02 (C-4′), 152.11

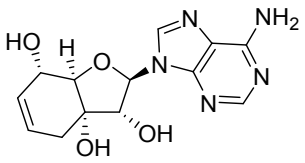
(C-2′), 164.87 (COO), 165.83 (CONH), 169.20 (3-OCOCH$_3$), 169.34 (3a-OCOCH$_3$). ESI MS, *m/z* (%): 635.2 (37) [M + Na + H], 634.2 (100) [M + Na], 612.2 (31) [M + H]. HRMS (ESI): calcd. for $C_{32}H_{30}O_8N_5$ [M + H] 612.20889; found: 612.20911; calcd. for $C_{32}H_{29}O_8N_5Na$ [M + Na] 634.19083; found: 634.19089.

(2*R*,3*R*,3a*R*,8*R*,8a*R*)-2-(6-Benzamido-9H-purin-9-yl)-8-(benzoyloxy)-3,3a,4,7,8,8a-hexahydro-2H-cyclohepta[b]furan-3,3a-diyl diacetate (12b)



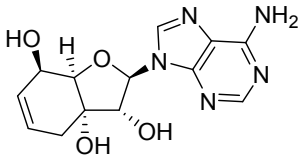
Yield 1.99 g (76%) of a white solid foam. $[\alpha]_D^{20}$ +25.0 (c = 0.428, $CHCl_3$). Found: C, 62.31; H, 4.90; N, 10.81. Calc. for $C_{32}H_{29}N_5O_8 \cdot 0.5\ CH_3COOC_2H_5$: C, 62.28; H, 5.07; N, 10.68%. ^{1}H NMR (500 MHz, d6-DMSO): δ 2.02 (s, 3 H, 3-OCOCH$_3$), 2.14 (s, 3 H, 3a-OCOCH$_3$), 2.54 (m, 1 H, H-7B), 2.89-3.02 (m, 2 H, H-4B, H-7A), 3.42 (dm, J_{gem} = 16.3, 1 H, H-4A), 4.87 (d, J_{8a-8} = 1.2, 1 H, H-8a), 5.63 (m, 1 H, H-5), 5.77-5.83 (m, 2 H, H-6, H-8), 6.29 (d, J_{3-2} = 7.2, 1 H, H-3), 6.37 (d, J_{2-3} = 7.2, 1 H, H-2), 7.51 (m, 2 H, m-benzoyl), 7.55 (m, 2 H, m-benzoylamino), 7.63-7.67 (m, 2 H, p-benzoylamino, p-benzoyl), 7.94 (m, 2 H, o-benzoyl), 8.04 (m, 2 H, o-benzoylamino), 8.61 (s, 1 H, H-2′), 8.64 (s, 1 H, H-8′), 11.27 (bs, 1 H, NH). ^{13}C NMR (125 MHz, d6-DMSO): δ 170.10 (3a-OCOCH$_3$), 169.59 (3a-OCOCH$_3$), 165.86 (CONH), 164.96 (COO), 152.34 (C-4′), 152.00 (C-2′), 150.88 (C-6′), 143.80 (C-8′), 133.72 (p-benzoyl), 133.44 (i-benzoylamino), 132.72 (p-benzoylamino), 129.61 (i-benzoyl), 129.50 (o-benzoyl), 128.97 (m-benzoyl), 128.69 (o-, m-benzoyl, C-6), 126.12 (C-5′), 123.20 (C-5), 84.71 (C-2), 84.70 (C-3a), 83.78 (C-8a), 73.83 (C-3), 70.34 (C-8), 31.19 (C-4), 29.94 (C-7), 21.71 (3a-OCO**C**H$_3$), 20.50 (3-OCO**C**H$_3$). HRMS (ESI): calcd. for $C_{32}H_{30}O_8N_5$ [M + H] 612.20889; found: 612.20890; calcd. for $C_{32}H_{29}O_8N_5Na$ [M + Na] 634.19083; found: 634.19062.

(2*R*,3*R*,3a*S*,7*S*,7a*R*)-2-(6-Amino-9*H*-purin-9-yl)-2,3,3a,4,7,7a-hexahydrobenzofuran-3,3a,7-triol (10a)



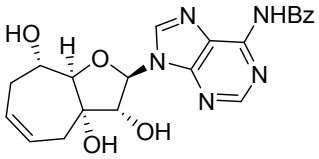
Yield 428 mg (68%) of a white crystals. M.p. 232-233.5 °C. $[\alpha]_D^{20}$ +30.4 (c = 0.289, DMF). Found: C, 49.78; H, 5.30; N, 22.28. Calc. for $C_{13}H_{15}N_5O_4 \cdot 0.5\ H_2O$: C, 49.68; H, 5.13; N, 22.15%. ^{1}H NMR (500 MHz, d6-DMSO): δ 0.52 (m, 1 H, H-4eq), 2.24 (dm, J_{gem} = 18.1, 1 H, H-4ax), 23.74 (d, J_{7a-7} = 6.2, 1 H, H-7a), 4.51 (m, 1 H, H-7), 4.82 (dd, J_{3-2} = 8.2, J_{3-OH} = 6.8, 1 H, H-3), 5.14 (d, J_{OH-7} = 5.9, 1 H, 7-OH), 5.16 (s, 1 H, 3a-OH), 5.51 (d, J_{OH-3} = 6.8, 1 H, 3-OH), 5.59 (dm, J_{6-5} = 10.0, 1 H, H-6), 5.66 (dm, J_{5-6} = 10.0, 1 H, H-5), 5.88 (d, J_{2-3} = 8.2, 1 H, H-2), 7.27 (d, 2 H, NH_2), 8.14 (s, 1 H, H-2′), 8.39 (s, 1 H, H-8′). ^{13}C NMR (125 MHz, d6-DMSO): δ 34.07 (C-4), 70.81 (C-7), 74.74 (C-3), 75.82 (C-3a), 86.18 (C-2), 88.99 (C-7a), 119.73 (C-5′), 124.53 (C-5), 130.40 (C-6), 141.14 (C-8′), 150.00 (C-4′), 152.73 (C-2′), 156.26 (C-6′). ESI MS, *m/z* (%): 329.2 (17) [M + Na + H], 328.2 (100) [M + Na], 306.2 (7) [M + H]. HRMS (ESI): calcd. for $C_{13}H_{15}O_4N_5Na$ [M + Na] 328.10163; found: 328.10159.

(2*R*,3*R*,3a*S*,7*R*,7a*R*)-2-(6-Amino-9*H*-purin-9-yl)-2,3,3a,4,7,7a-hexahydrobenzofuran-3,3a,7-triol (10b)



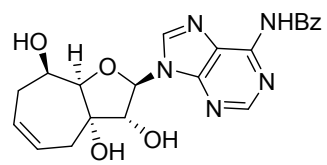
Yield 570 mg (92%) of a white crystals. M.p. 245.5-247 °C. $[\alpha]_D^{20}$ -60.8 (c = 0.311, DMF). Found: C, 50.60; H, 5.07; N, 22.57. Calc. for $C_{13}H_{15}N_5O_4 \cdot 0.25\ H_2O$: C, 50.40; H, 5.04; N, 22.61%. ^{1}H NMR (500 MHz, d6-DMSO): δ 2.16 (dm, J_{gem} = 17.5, 1 H, H-4ax), 2.55 (dm, J_{gem} = 17.5, 1 H, H-4eq), 3.94 (d, $J_{7a\text{-}7}$ = 4.5, 1 H, H-7a), 4.20 (q, $J_{7\text{-}7a} = J_{7\text{-}OH}$ = 4.5, 1 H, H-7), 4.30 (t, $J_{3\text{-}2} = J_{3,OH}$ = 7.3, 1 H, H-3), 5.11 (s,1 H, 3a-OH), 5.53 (d, $J_{OH\text{-}3}$ = 6.7, 1 H, 3-OH), 5.60 (d, $J_{OH\text{-}7}$ = 4.3, 1 H, 7-OH), 5.85 (d, $J_{2\text{-}3}$ = 7.9, 1 H, H-2), 5.86 (m, 1 H, H-5), 5.90 (m, 1 H, H-6), 7.34 (d, 2 H, NH_2), 8.13 (s, 1 H, H-2′), 8.29 (s, 1 H, H-8′). ^{13}C NMR (125 MHz, d6-DMSO): δ 34.92 (C-4), 64.69 (C-7), 74.24 (C-3a), 78.15 (C-3), 85.79, 85.88 (C-2, C-7a), 119.30 (C-5′), 127.49 (C-5), 129.45 (C-6), 139.83 (C-8′), 149.73 (C-4′), 152.62 (C-2′), 156.32 (C-6′). ESI MS, *m/z* (%): 329.2 (16) [M + Na + H], 328.2 (100) [M + Na], 306.2 (8) [M + H]. HRMS (ESI): calcd. for $C_{13}H_{15}O_4N_5Na$ [M + Na] 328.10163; found: 328.10154.

(2*R*,3*R*,3a*S*,8*S*,8a*R*)-2-(6-Amino-9*H*-purin-9-yl)-3,3a,4,7,8,8a-hexahydro-2H-cyclohepta[b]furan-3,3a,8-triol (13a)



Yield 509 mg (80%) of a white crystals. M.p. 205.5-207 °C. $[\alpha]_D^{20}$ +0.5 (c = 0.389, DMF). Found: C, 52.48; H, 5.40; N, 21.65. Calc. for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93%. HRMS (ESI): calcd. for $C_{14}H_{17}O_4N_5Na$ [M + Na] 342.11728; found: 342.11724. ^{1}H NMR (500 MHz, d6-DMSO): δ 2.22 (m, 1 H, H-7B), 2.40-2.49 (m, 3 H, 2 × H-4, H-7A), 3.72 (d, $J_{8a\text{-}8}$ = 8.1, 1 H, H-8a), 3.92 (m, 1 H, H-8), 4.53 (m, 1 H, H-3), 4.84 (s, 1 H, 3a-OH), 4.89 (d, $J_{OH\text{-}8}$ = 4.2, 1 H, 8-OH), 5.47-5.53 (m, 2 H, H-5, 3-OH), 5.60 (m, 1 H, H-6), 5.78 (d, $J_{2\text{-}3}$ = 7.9, 1 H, H-2), 7.30 (brs, 2H, NH_2), 8.14 (s, 1 H, H-2′), 8.35 (s, 1 H, H-8′). ^{13}C NMR (125 MHz, d6-DMSO): δ 33.60 (C-4), 34.42 (C-7), 68.57 (C-8), 70.86 (C-3a), 75.44 (C-3), 86.21 (C-2), 90.56 (C-8a), 119.54 (C-5′), 124.99 (C-5), 128.04 (C-6), 140.43 (C-8′), 149.93 (C-4′), 152.82 (C-2′), 156.29 (C-6′). ESI MS, *m/z* (%): 343.1 (18) [M + Na + H], 342.1 (100) [M + Na], 320.1 (10) [M + H].

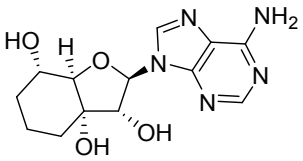
(2*R*,3*R*,3a*S*,8*R*,8a*R*)-2-(6-Amino-9*H*-purin-9-yl)-3,3a,4,7,8,8a-hexahydro-2*H*-cyclohepta[b]furan-3,3a,8-triol (13b)



Yield 467 mg (66%) of a white crystals. M.p. 255-256 °C. $[\alpha]_D^{20}$ -25.5 (c = 0.364, DMF). Found: C, 52.30; H, 5.51; N, 21.61. Calc. for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93%. ^{1}H NMR (500 MHz, d6-DMSO, 60 °C): δ 2.30-2.37 (m, 2 H, H-4b, H-7b), 2.47 (m, 1 H, H-7a), 2.75 (dm, J_{gem} = 14.9, 1 H, H-4a), 4.05 (d, $J_{8a\text{-}8}$ = 1.6, 1 H, H-8a), 4.08 (m, 1 H, H-8), 4.55 (bs, 1 H, 3a-OH), 4.60 (dd, $J_{3\text{-}2}$ = 8.1, $J_{3\text{-}OH}$ = 6.7, 1 H, H-3), 5.32 (d, $J_{OH\text{-}3}$ = 6.7, 1 H, 3-OH), 5.53-5.62 (m, 2 H, H-5, H-6), 5.80 (d, $J_{2\text{-}3}$ = 8.1, 1 H, H-2), 5.85 (bs, 1 H, 8-OH), 7.19 (s, 2 H, NH_2), 8.15 (s,

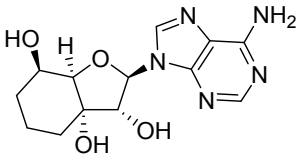
1 H, H-2′), 8.25 (s, 1H, H-8′). ^{13}C NMR (125 MHz, d6-DMSO): δ 33.20 (C-4), 33.73 (C-7), 68.26 (C-8), 75.78 (C-3), 79.58 (C-3a), 86.80 (C-2), 89.65 (C-8a), 119.74 (C-5′), 124.49 (C-5), 128.42 (C-6), 140.26 (C-8′), 149.14 (C-4′), 152.17 (C-2′), 156.28 (C-6′). ESI MS, *m/z* (%): 343.1 (15) [M + Na + H], 342.1 (100) [M + Na], 320.1 (36) [M + H]. HRMS (ESI): calcd. for $C_{14}H_{18}O_4N_5$ [M + H] 320.13533; found: 320.13536; calcd. for $C_{14}H_{17}O_4N_5Na$ [M + Na] 342.11728; found: 342.11727.

(2*R*,3*R*,3a*S*,7*S*,7a*R*)-2-(6-Amino-9*H*-purin-9-yl)octahydrobenzofuran-3,3a,7-triol (11a)



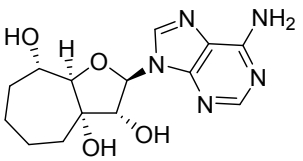
Yield 102 mg (66%) of a white crystals. M.p. 234-236 °C. $[\alpha]_D^{20}$ -9.4 (c = 0.415, DMF). Found: C, 50.62; H, 5.63; N, 22.65. Calc. for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.13 (m, 1 H, H-6ax), 1.47-1.35 (m, 2 H, H-4ax, H-5ax), 1.56 (m, 1 H, H-5eq), 1.75 (m, 1 H, H-6eq), 1.99 (m, 1 H, H-4eq), 3.54 (d, $J_{7a\text{-}7}$ = 8.1, 1 H, H-7a), 3.86 (m, 1 H, H-7), 4.82 (d, $J_{OH\text{-}7}$ = 5.1, 1 H, 7-OH), 4.92 (dd, $J_{3\text{-}2}$ = 8.1, $J_{3\text{-}OH}$ = 5.7, 1 H, H-3), 5.01 (s, 1 H, 3a-OH), 5.36 (bd, $J_{OH\text{-}3}$ = 5.7, 1 H, 3-OH), 5.98 (d, $J_{2\text{-}3}$ = 8.1, 1 H, H-2), 7.26 (brs, 2H, NH_2), 8.16 (s, 1 H, H-2′), 8.46 (s, 1 H, H-8′). ^{13}C NMR (125 MHz, d6-DMSO): δ 19.24 (C-5), 32.26 (C-4), 32.74 (C-6), 72.29 and 72.32 (C-3, C-7), 77.59 (C-3a), 86.93 (C-2), 90.55 (C-7a), 119.61 (C-5′), 140.94 (C-8′), 150.23 (C-4′), 152.78 (C-2′), 156.25 (C-6′). HRMS (ESI): calcd. for $C_{13}H_{18}O_4N_5$ [M + H] 308.13533; found: 308.13522.

(2*R*,3*R*,3a*S*,7*R*,7a*R*)-2-(6-Amino-9*H*-purin-9-yl)octahydrobenzofuran-3,3a,7-triol (11b)



Yield 107 mg (70%) of a white crystals. M.p. 257-259 °C. $[\alpha]_D^{20}$ -43.5 (c = 0.352, methanol). Found: C, 50.78; H, 5.62; N, 22.53. Calc. for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79%. ^{1}H NMR (600 MHz, d6-DMSO): δ 1.36-1.47 (m, 3 H, H-4ax, H-5b, H-6b), 1.61-1.69 (m, 2H, H-5a, H-5b), 1.95 (m, 1 H, H-4eq), 3.80 (d, $J_{7a\text{-}7}$ = 4.3, 1 H, H-7a), 3.90 (m, 1 H, H-7), 4.45 (t, $J_{3\text{-}OH}$ = $J_{3\text{-}2}$ = 6.7, 1 H, H-3), 4.88 (s, 1 H, 3a-OH), 5.36 (d, $J_{OH\text{-}3}$ = 6.5, 1 H, 3-OH), 5.57 (d, $J_{OH\text{-}7}$ = 3.6, 1 H, 7-OH), 5.94 (d, $J_{2\text{-}3}$ = 7.1, 1 H, H-2), 7.32 (brs, 2H, NH_2), 8.14 (s, 1 H, H-2′), 8.41 (s, 1 H, H-8′). ^{13}C NMR (151 MHz, d6-DMSO): δ 16.37 (C-5), 29.62 (C-6), 32.26 (C-4), 66.09 (C-7), 75.29 (C-3), 76.06 (C-3a), 84.79 (C-7a), 87.43 (C-2), 119.18 (C-5′), 140.03 (C-8′), 149.91 (C-4′), 152.62 (C-2′), 156.29 (C-6′). ESI MS, *m/z* (%): 331.1 (17) [M + Na + H], 330.1 (100) [M + Na], 308.1 (13) [M + H]. HRMS (ESI): calcd. for $C_{13}H_{18}O_4N_5$ [M + H] 308.13533; found: 308.13524; calcd. for $C_{13}H_{17}O_4N_5Na$ [M + Na] 330.11728; found: 330.11727.

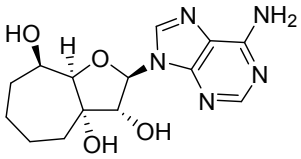
(2*R*,3*R*,3a*S*,8*S*,8a*R*)-2-(6-Amino-9*H*-purin-9-yl)octahydro-2*H*-cyclohepta[b]furan-3,3a,8-triol (14a)



Yield 126 mg (78%) of a white crystals. M.p. 184-187 °C. $[\alpha]_D^{20}$ -7.0 (c = 0.257, DMF). Found: C, 49.60; H, 6.05; N, 20.38. Calc. for

$C_{13}H_{17}N_5O_4 \cdot H_2O$: C, 49.55; H, 6.24; N, 20.64%. ESI MS, *m/z* (%): 345.3 (18) [M + Na + H], 344.3 (100) [M + Na]. ^{1}H NMR (500 MHz, d6-DMSO, 60 °C): δ 1.32 (m, 1 H, H-6b), 1.41-1.54 (m, 4 H, H-4b, H-5, H-7b), 1.71 (dm, J_{gem} = 13.4, 1 H, H-6a), 1.81 (dm, J_{gem} = 13.6, 1 H, H-7a), 1.92 (m, 1 H, H-4a), 3.63 (d, $J_{8a\text{-}8}$ = 9.4, 1 H, H-8a), 3.65 (dm, $J_{8\text{-}8a}$ = 9.4, 1 H, H-8), 4.36 (d, $J_{3\text{-}2}$ = 8.3, 1 H, H-3), 4.42, 4.61, 5.51 (3 x bs, 3 H, 3-OH, 3a-OH, 8-OH), 5.78 (d, $J_{2\text{-}3}$ = 8.3, 1 H, H-2), 7.28 (bs, 2 H, NH_2), 8.15 (s, 1 H, H-2′), 8.39 (s, 1 H, H-8′). ^{13}C NMR (125 MHz, d6-DMSO): δ 21.72 (C-5), 26.69 (C-6), 35.27 (C-7), 35.73 (C-4), 70.85 (C-8), 76.62 (C-3a), 77.61 (C-3), 85.16 (C-2), 92.31 (C-8a), 119.42 (C-5′), 140.20 (C-8′), 150.02 (C-4′), 152.81 (C-2′), 156.26 (C-6′). HRMS (ESI): calcd. for $C_{14}H_{19}O_4N_5Na$ [M + Na] 344.13293; found: 344.13287.

(2*R*,3*R*,3a*S*,8*R*,8a*R*)-2-(6-Amino-9*H*-purin-9-yl)octahydro-2*H*-cyclohepta[b]furan-3,3a,8-triol (14b)



Yield 120 mg (75%) of a white crystals. M.p. 252.5-253.5 °C. $[\alpha]_D^{20}$ -71.5 (c = 0.435, DMF). Found: C, 52.10; H, 5.85; N, 21.56. Calc. for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.79%. ^{1}H NMR (500 MHz, d6-DMSO): δ 1.40-1.48 (m, 2 H, H-5b, H-7b), 1.56-1.64 (m, 3 H, H-5a, H-6), 1.81-1.91 (m, 3 H, H-4, H-7a), 3.95-3.97 (m, 2 H, H-8, H-8a), 4.43 (dd, $J_{3\text{-}2}$ = 8.0, $J_{3\text{-}OH}$ = 6.0, 1 H, H-3), 4.45 (s, 1 H, 3a-OH), 5.45 (d, $J_{OH\text{-}3}$ = 6.0, 1 H, 3-OH), 5.75 (d, $J_{2\text{-}3}$ = 8.0, 1 H, H-2), 6.52 (bs, 1 H, 8-OH), 7.46 (bs, 2 H, NH_2), 8.13 (s, 1 H, H-2′), 8.30 (s, 1H, H-8′). ^{13}C NMR (125 MHz, d6-DMSO): δ 22.85 (C-5), 24.87 (C-6), 31.80 (C-7), 36.31 (C-4), 70.91 (C-8), 78.04 (C-3), 79.40 (C-3a), 88.56 (C-2), 92.48 (C-8a), 120.20 (C-5′), 141.17 (C-8′), 148.56 (C-4′), 152.16 (C-2′), 156.62 (C-6′). ESI MS, *m/z* (%): 345.2 (18) [M + Na + H], 344.2 (100) [M + Na], 322.3 (17) [M + H]. HRMS (ESI): calcd. for $C_{17}H_{22}O_4N_5$ [M + H] 344.13293; found: 344.13304.

In situ structure determination of intermediate 20b (supplementary figures)

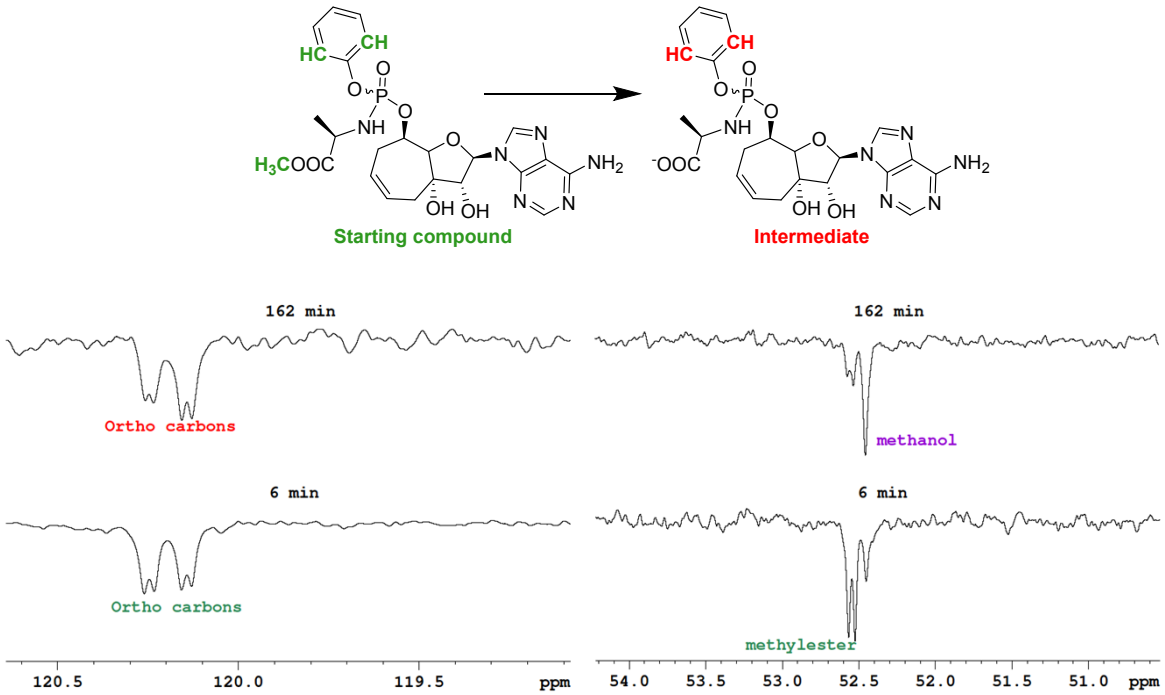


Figure S1. ^{13}C NMR spectra of *ortho* carbons (left) and methoxy group (right) of compound **17b**. ^{13}C NMR spectra were accumulated at intervals 6-57 min (bottom) and 162-213 min (top) after the start of the chemical hydrolysis.

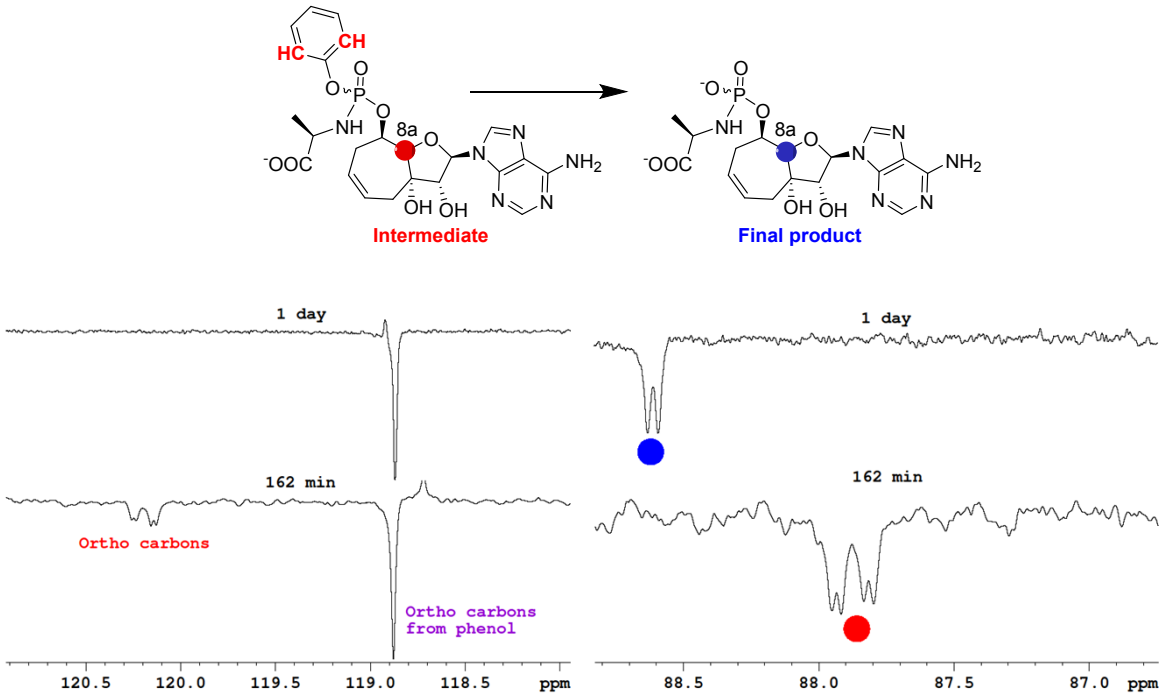


Figure S2. ^{13}C NMR spectra of *ortho* carbons (left) and of carbon 8a (right).

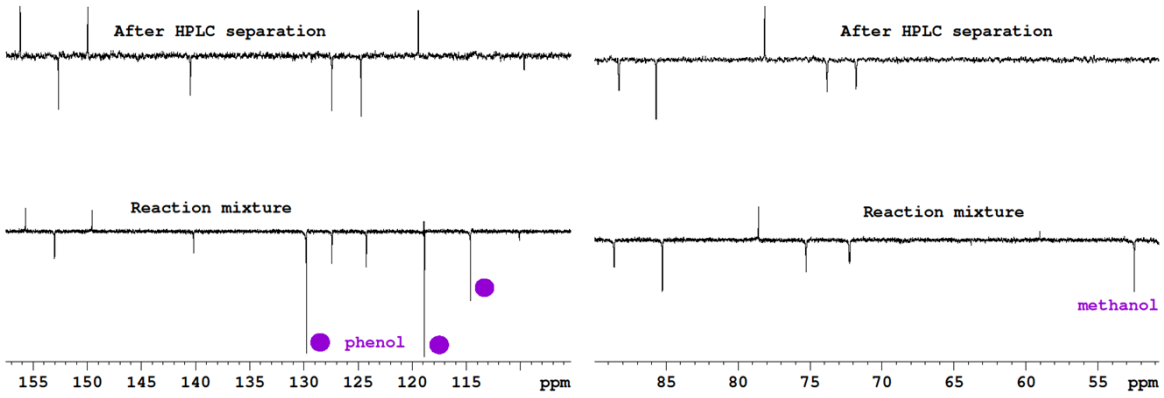
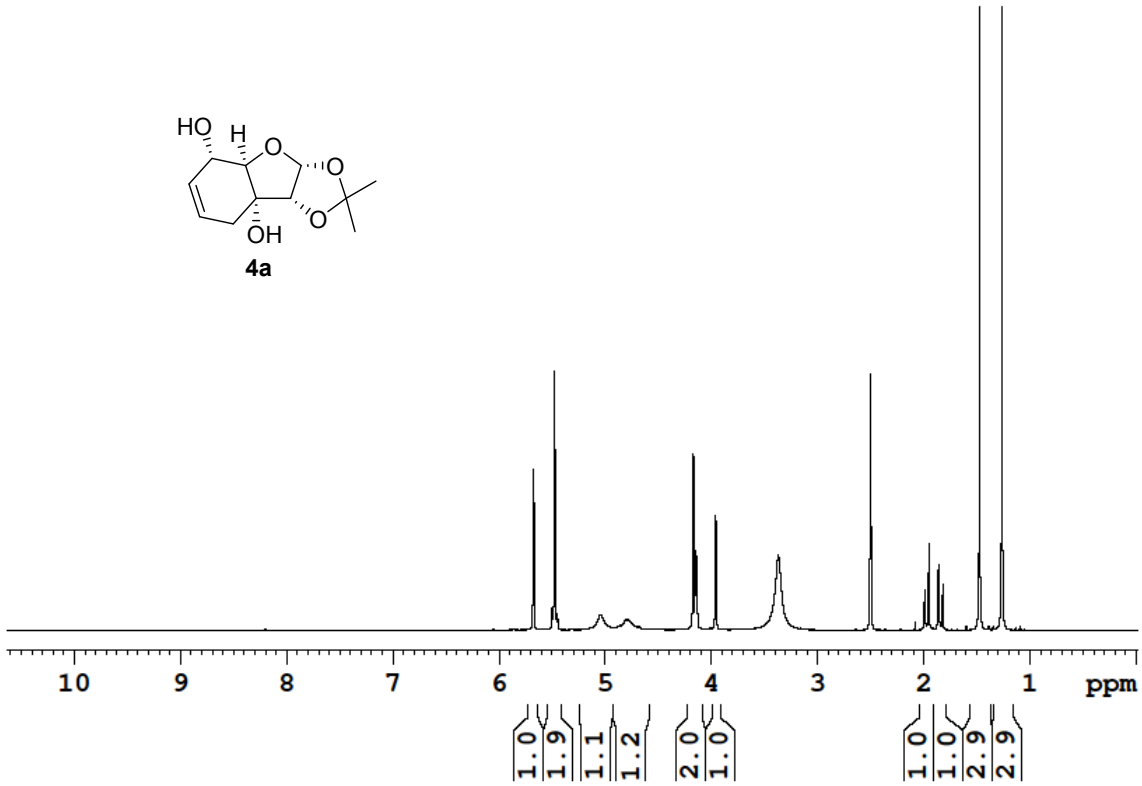
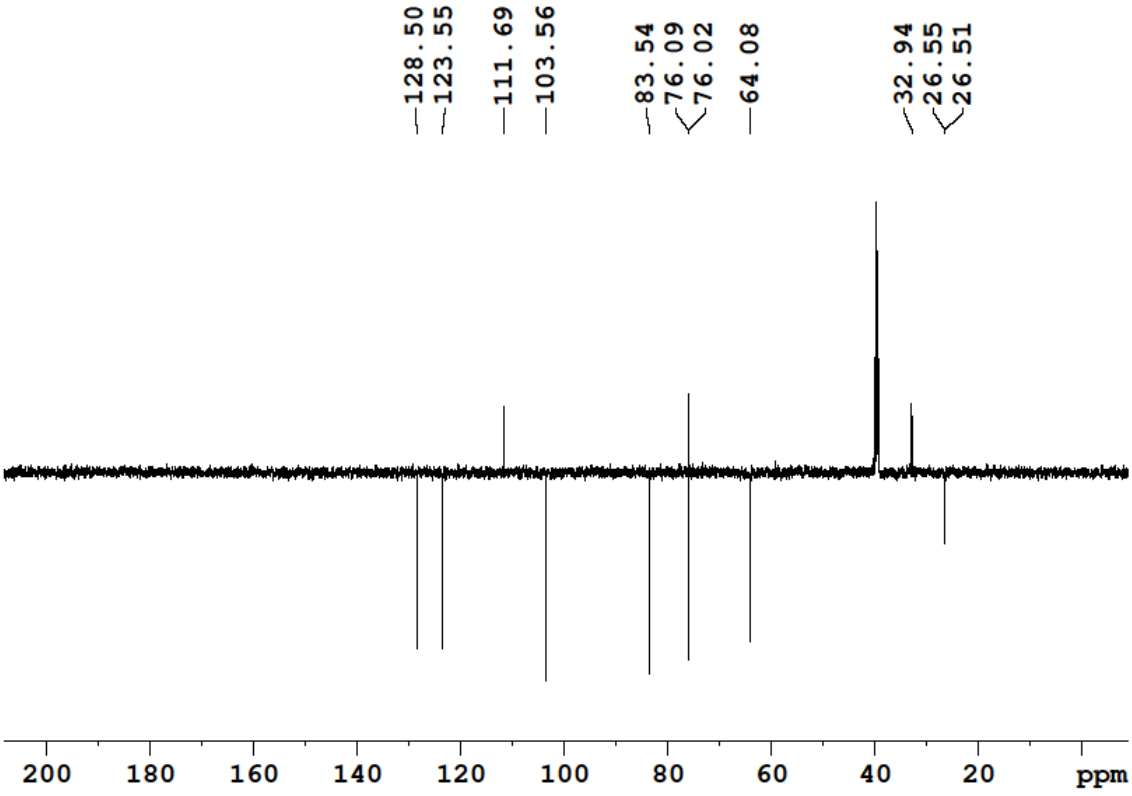


Figure S3. Aromatic region (left) and aliphatic region (right) of ^{13}C NMR spectra of the reaction mixture after chemical hydrolysis of compound **17a** (bottom) and the reaction mixture after HPLC separation (top). NMR signals of phenol and methanol disappeared.

HO
H
O
O
O
OH

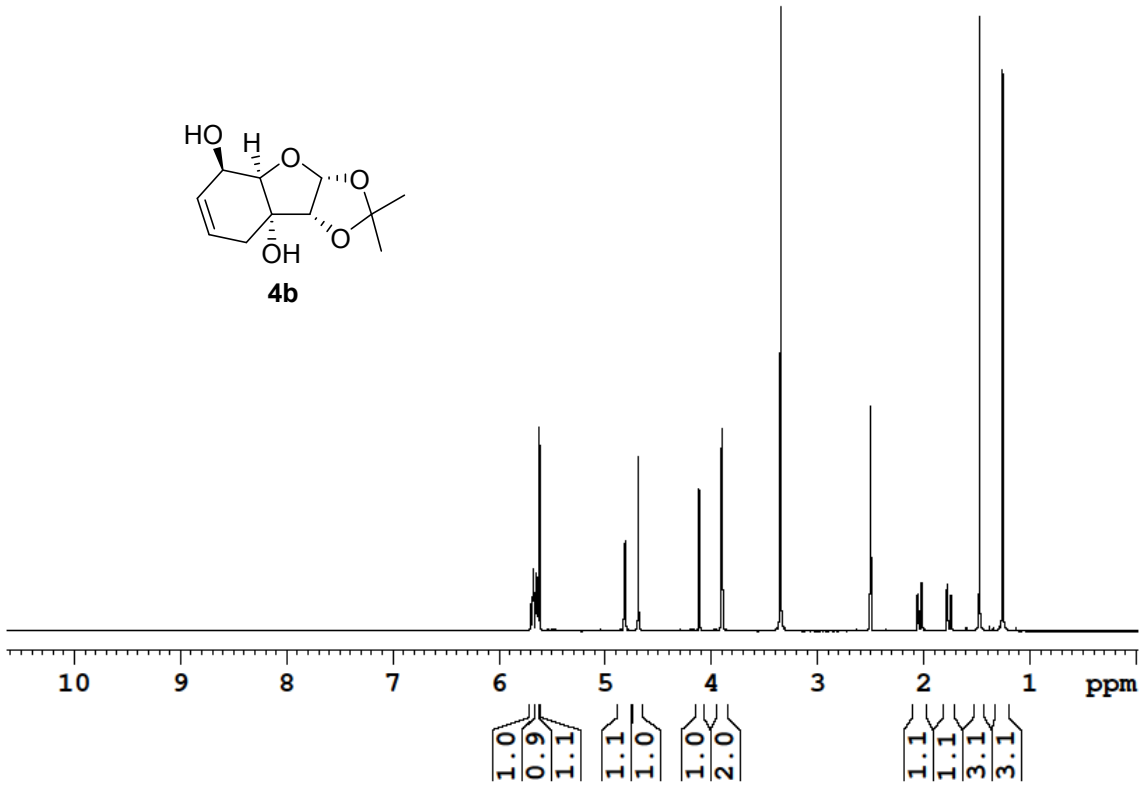
4a

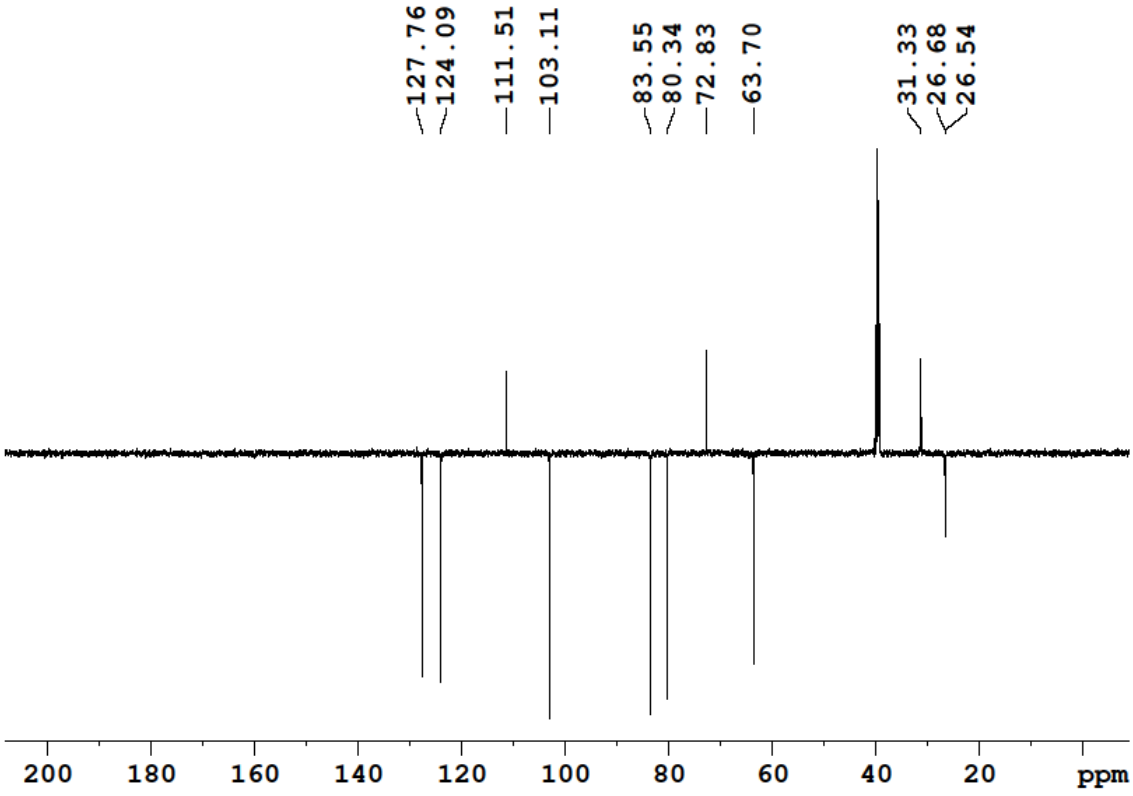

10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.9
1.1
1.2
2.0
1.0
1.0
1.0
2.9
2.9

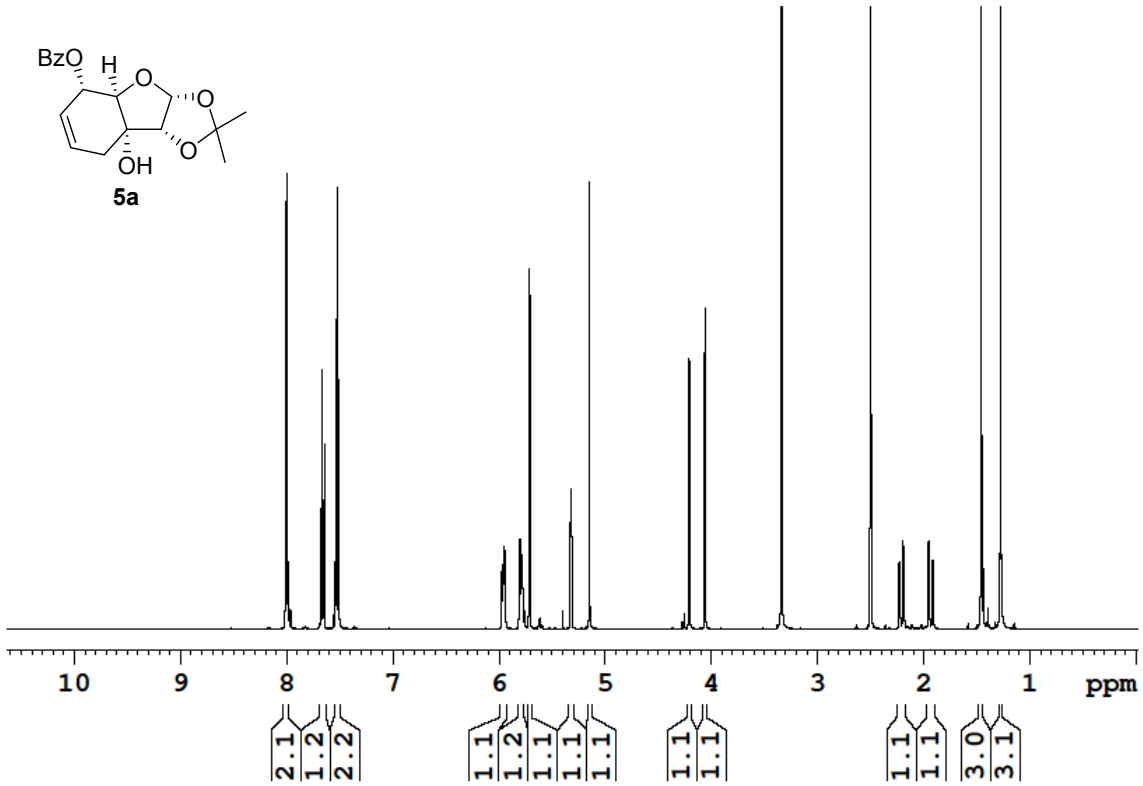

128.50
123.55
111.69
103.56
83.54
76.09
76.02
64.08
32.94
26.55
26.51
200
180
160
140
120
100
80
60
40
20
ppm

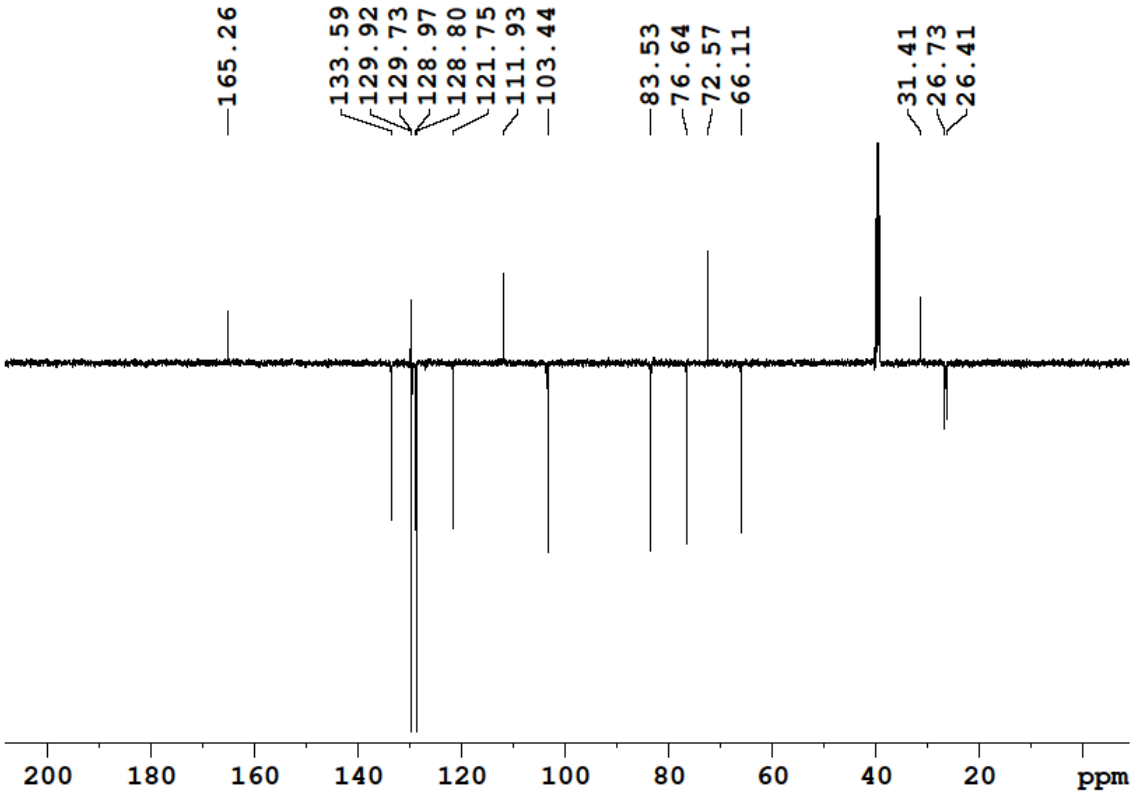
HO
H
O
O
O
OH

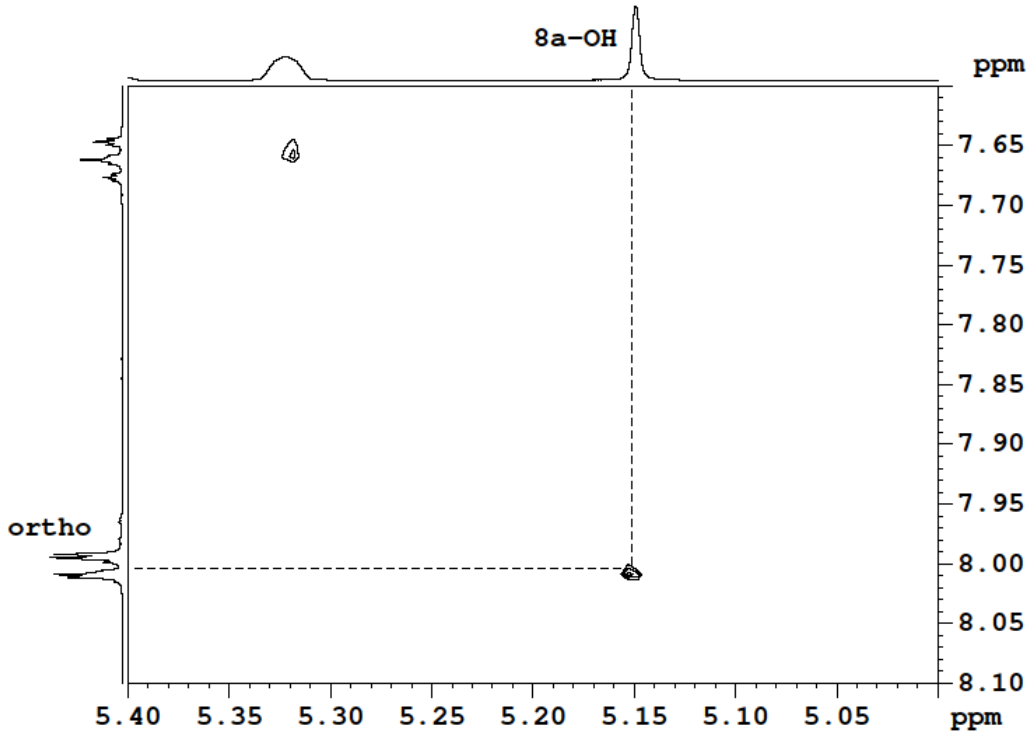
4b


10
9
8
7
6
5
4
3
2
1
ppm
1.0
0.9
1.1
1.1
1.0
1.0
2.0
1.1
1.1
3.1
3.1


127.76
124.09
111.51
103.11
83.55
80.34
72.83
63.70
31.33
26.68
26.54
200
180
160
140
120
100
80
60
40
20
ppm

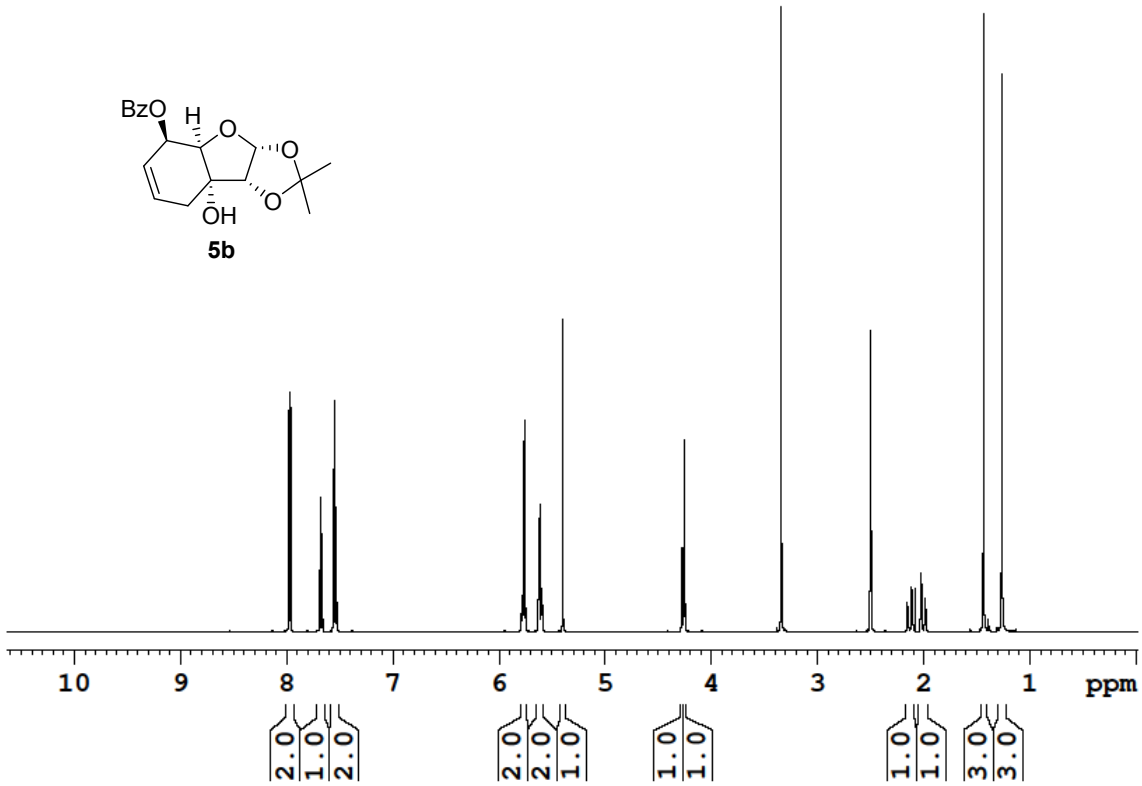

BzO
H
O
O
O
OH
5a
10
9
8
7
6
5
4
3
2
1
ppm
2.1
1.2
2.2
1.1
1.2
1.1
1.1
1.1
1.1
1.1
1.1
3.0
3.1

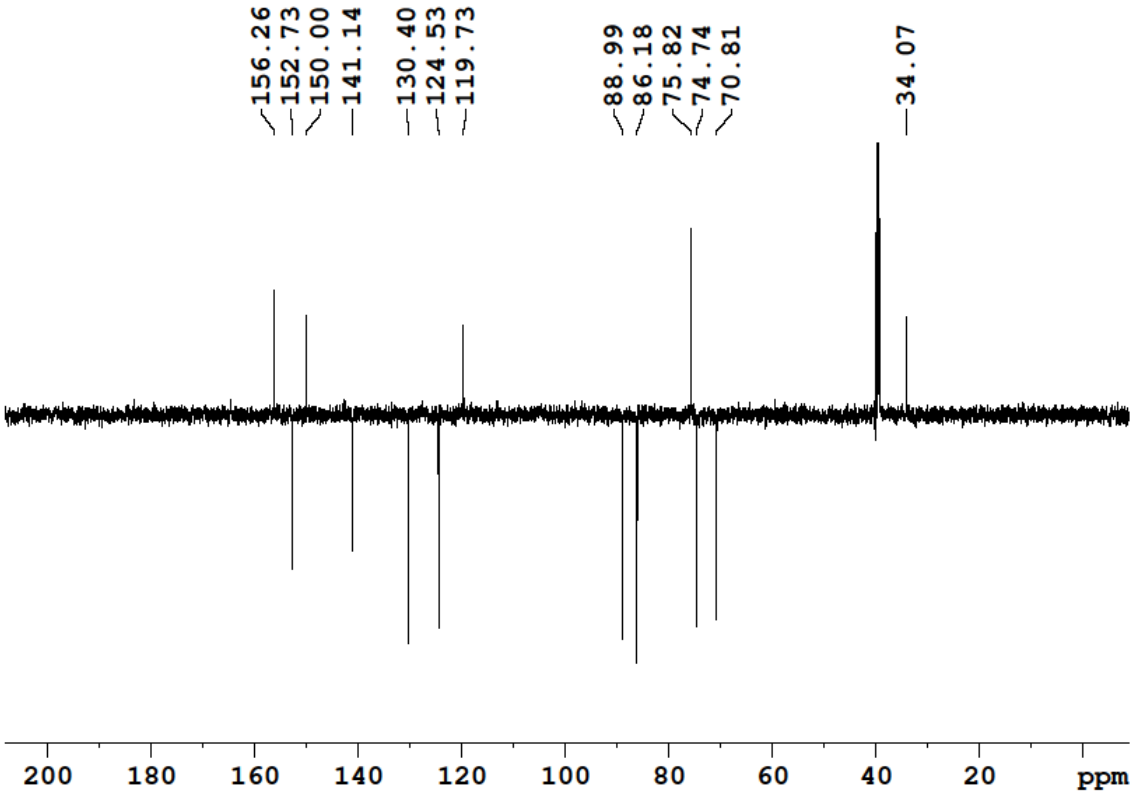

165.26
133.59
129.92
129.73
128.97
128.80
121.75
111.93
103.44
83.53
76.64
72.57
66.11
31.41
26.73
26.41
200
180
160
140
120
100
80
60
40
20
ppm


8a-OH
ppm
7.65
7.70
7.75
7.80
7.85
7.90
7.95
8.00
8.05
8.10
ortho
5.40
5.35
5.30
5.25
5.20
5.15
5.10
5.05
ppm

BzO
H
O
O
O
OH

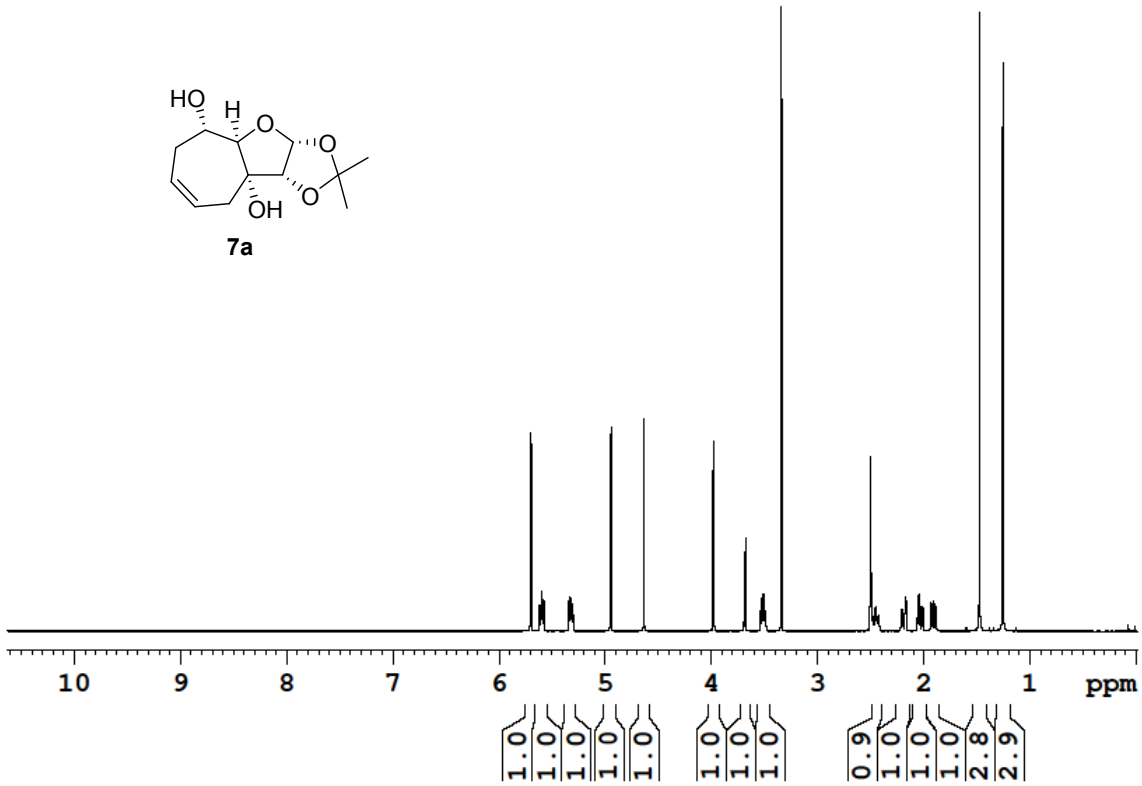
5b

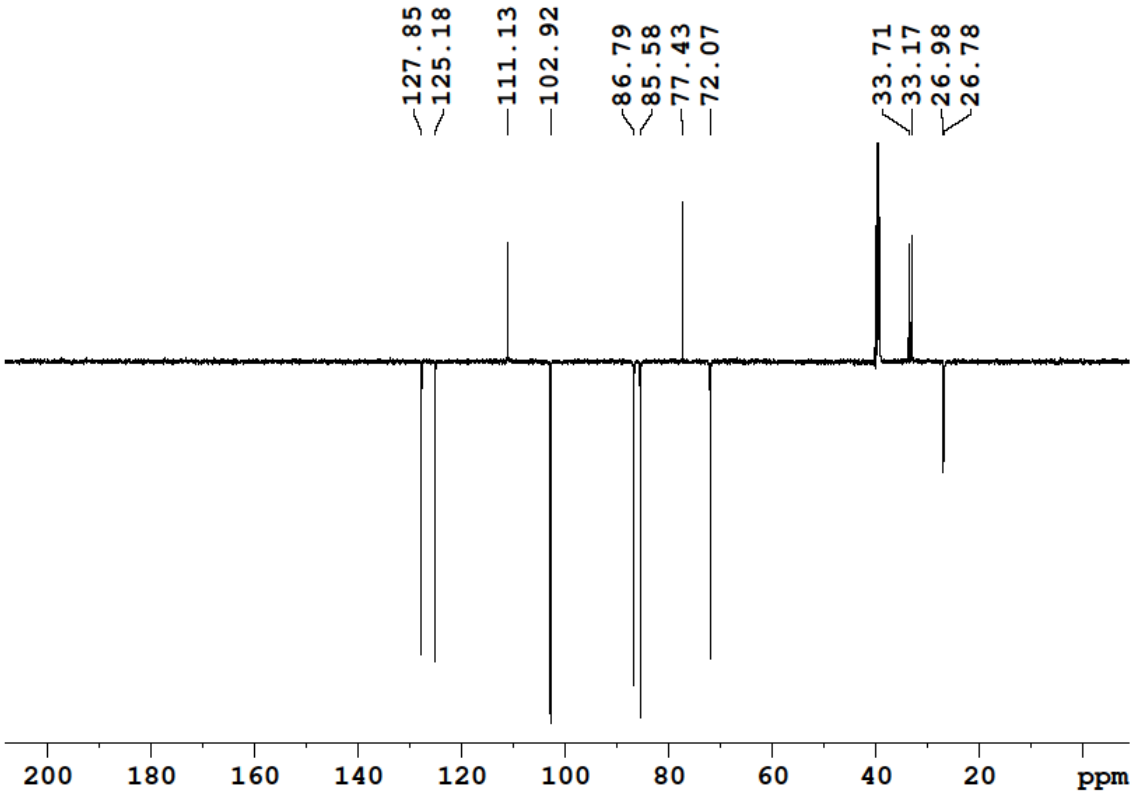

10
9
8
7
6
5
4
3
2
1
ppm
2.0
1.0
2.0
2.0
2.0
1.0
1.0
1.0
1.0
1.0
3.0
3.0


156.26
152.73
150.00
141.14
130.40
124.53
119.73
88.99
86.18
75.82
74.74
70.81
34.07
200
180
160
140
120
100
80
60
40
20
ppm

HO
H
O
O
O
OH

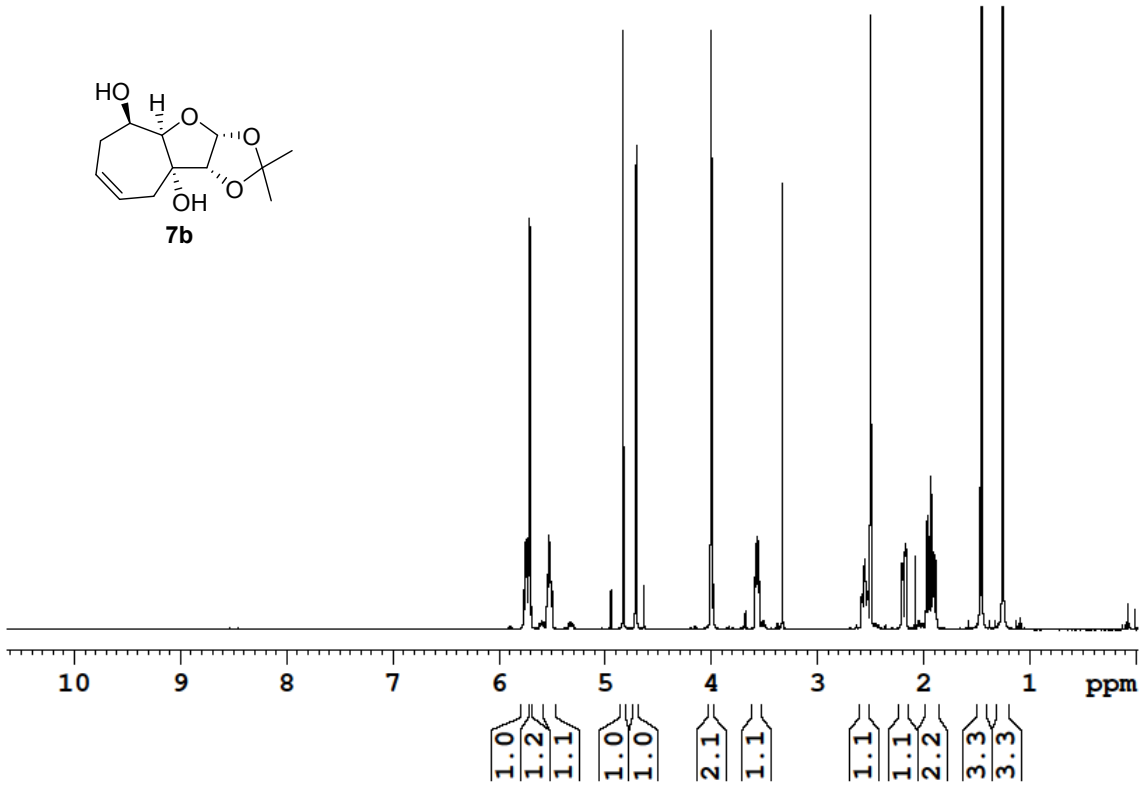
7a

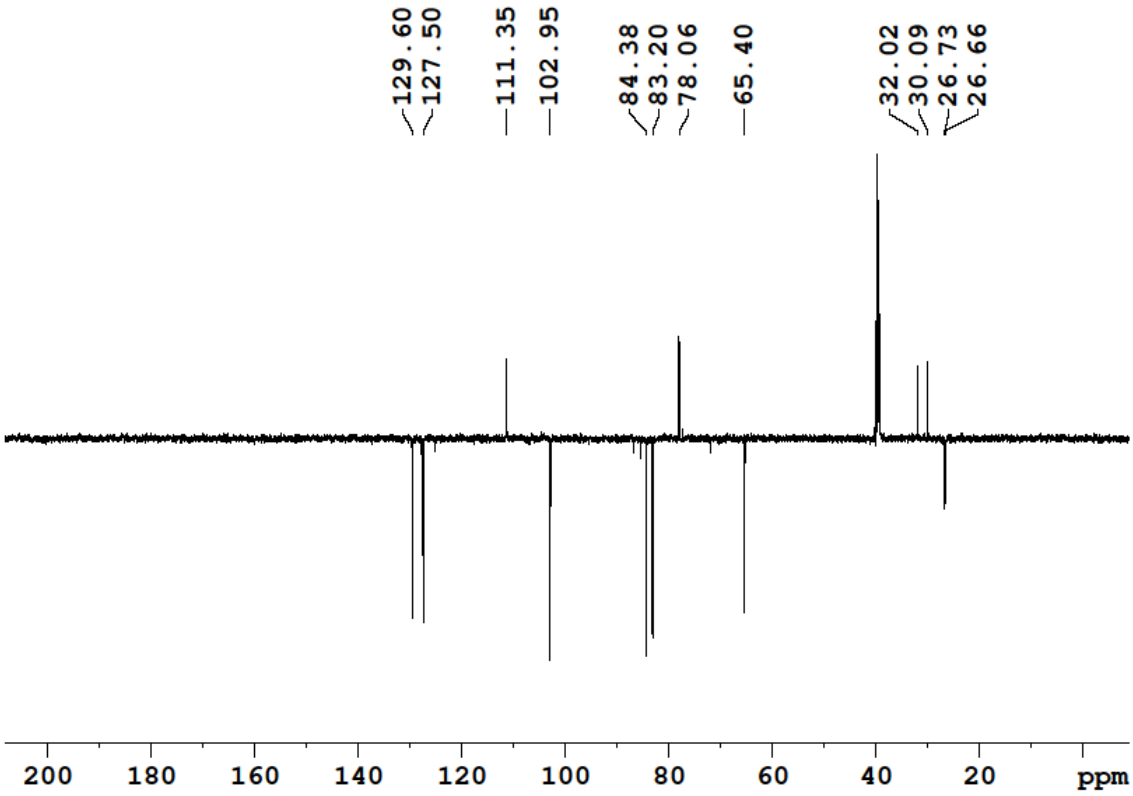

10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
0.9
1.0
1.0
1.0
2.8
2.9


127.85
125.18
111.13
102.92
86.79
85.58
77.43
72.07
33.71
33.17
26.98
26.78
200
180
160
140
120
100
80
60
40
20
ppm

HO
H
O
O
O
OH

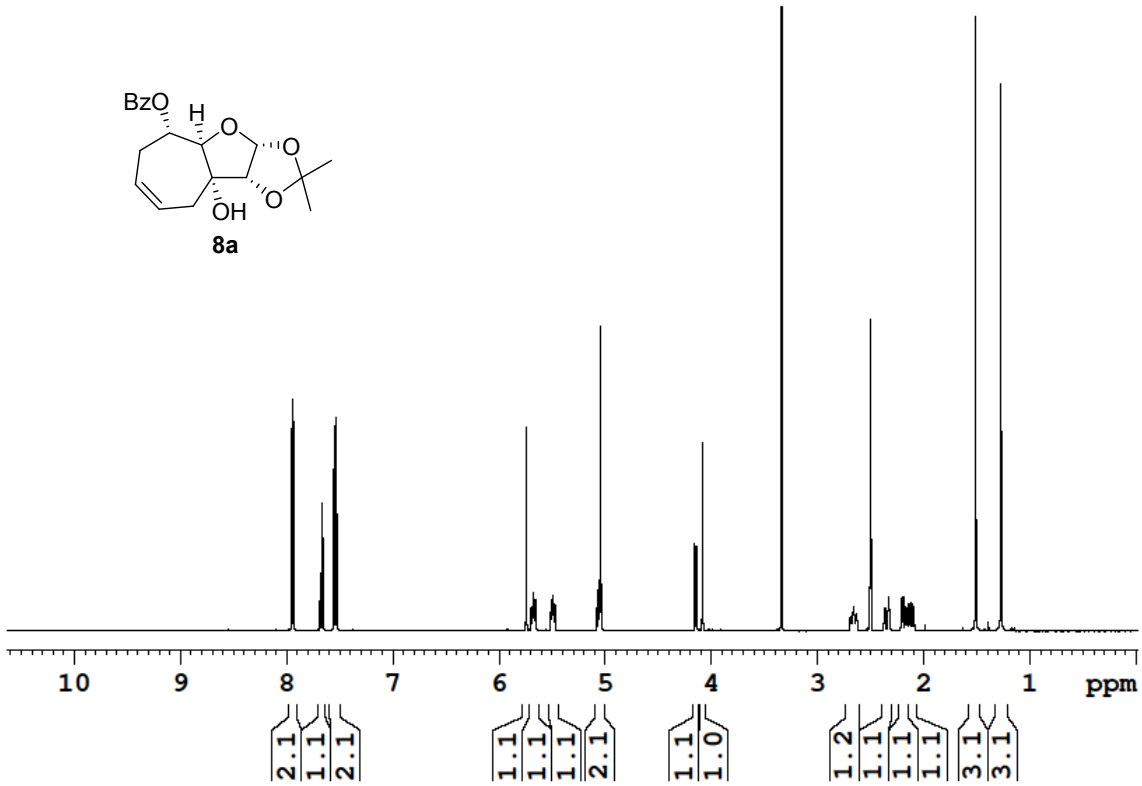
7b

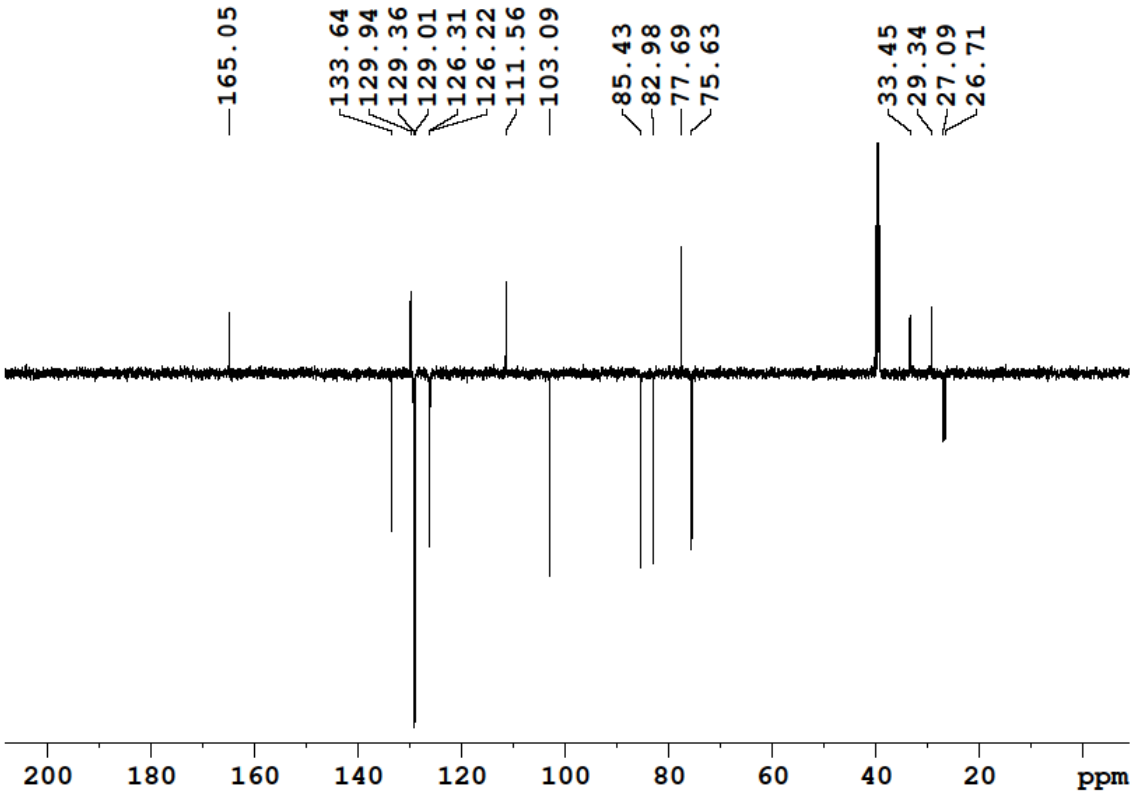

10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.2
1.1
1.0
1.0
2.1
1.1
1.1
1.1
2.2
3.3
3.3

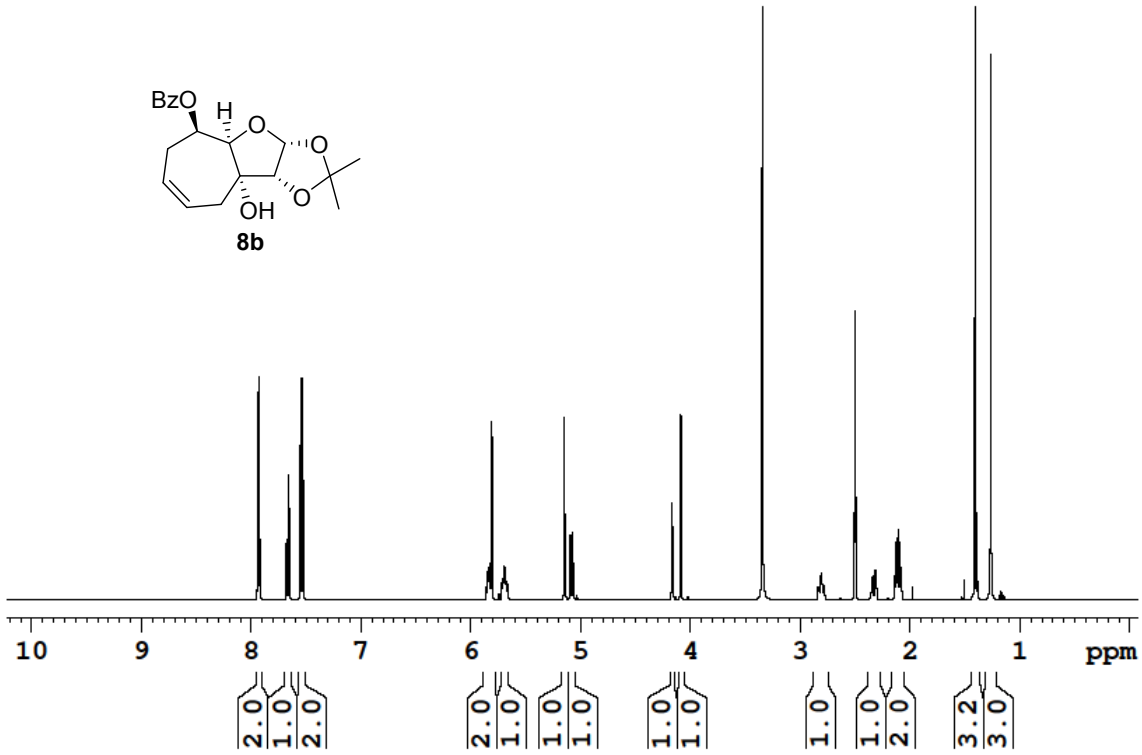

129.60
127.50
111.35
102.95
84.38
83.20
78.06
65.40
32.02
30.09
26.73
26.66
200
180
160
140
120
100
80
60
40
20
ppm

BzO
H
O
O
O
OH

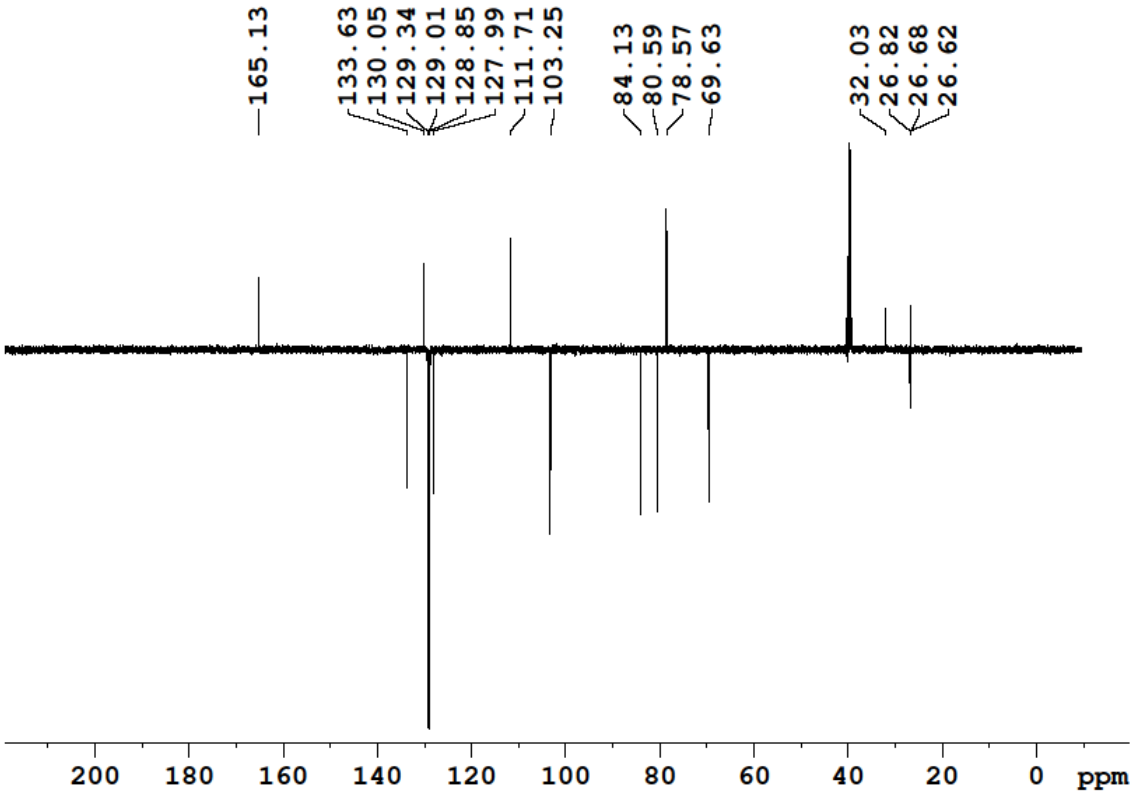
8a

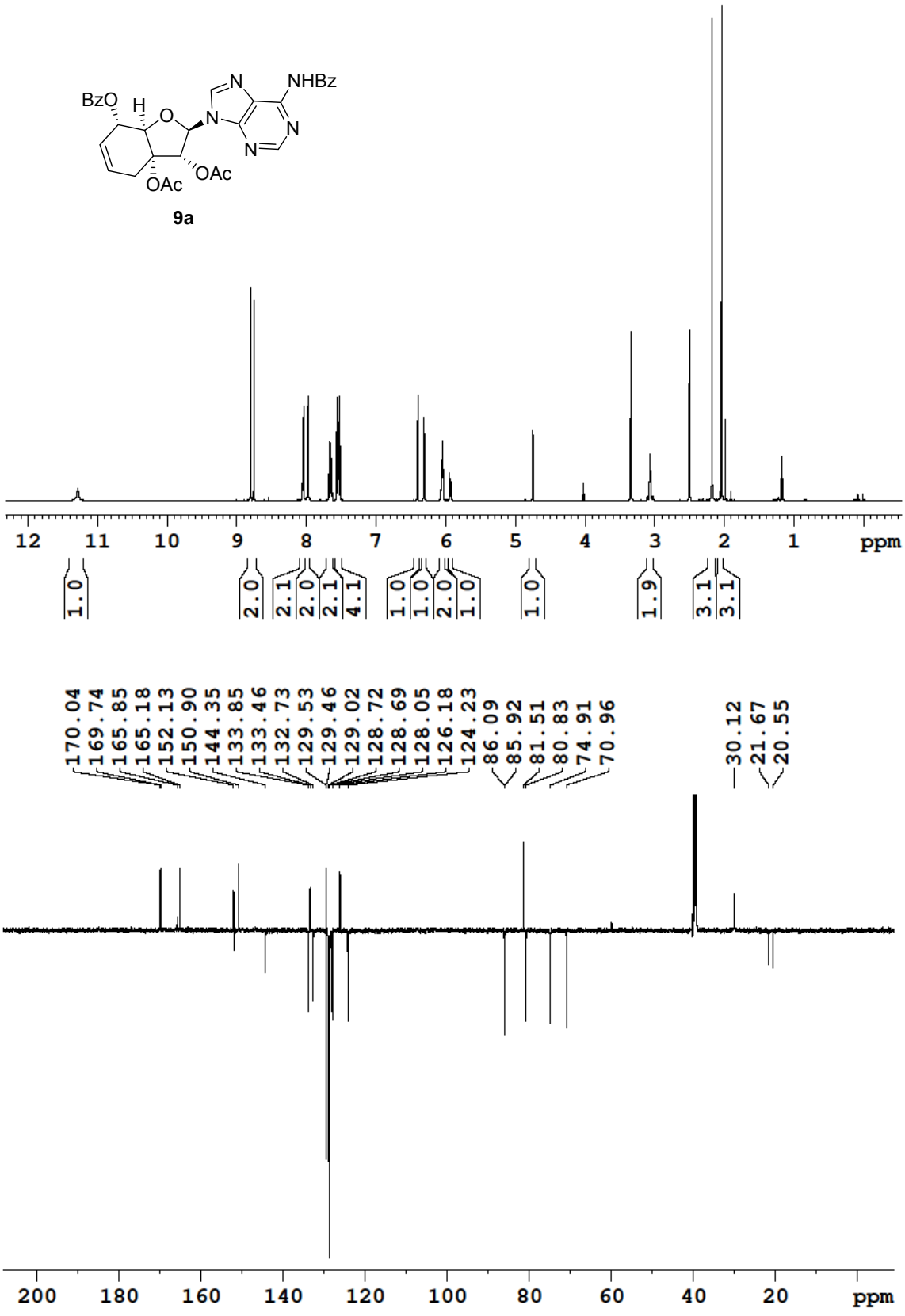

10
9
8
7
6
5
4
3
2
1
ppm
2.1
1.1
2.1
1.1
1.1
1.1
2.1
1.1
1.0
1.2
1.1
1.1
1.1
3.1
3.1


165.05
133.64
129.94
129.36
129.01
126.31
126.22
111.56
103.09
85.43
82.98
77.69
75.63
33.45
29.34
27.09
26.71
200
180
160
140
120
100
80
60
40
20
ppm


BzO
H
O
O
O
OH
10
9
8
7
6
5
4
3
2
1
ppm
2.0
1.0
2.0
2.0
1.0
1.0
1.0
1.0
1.0
1.0
2.0
3.2
3.0

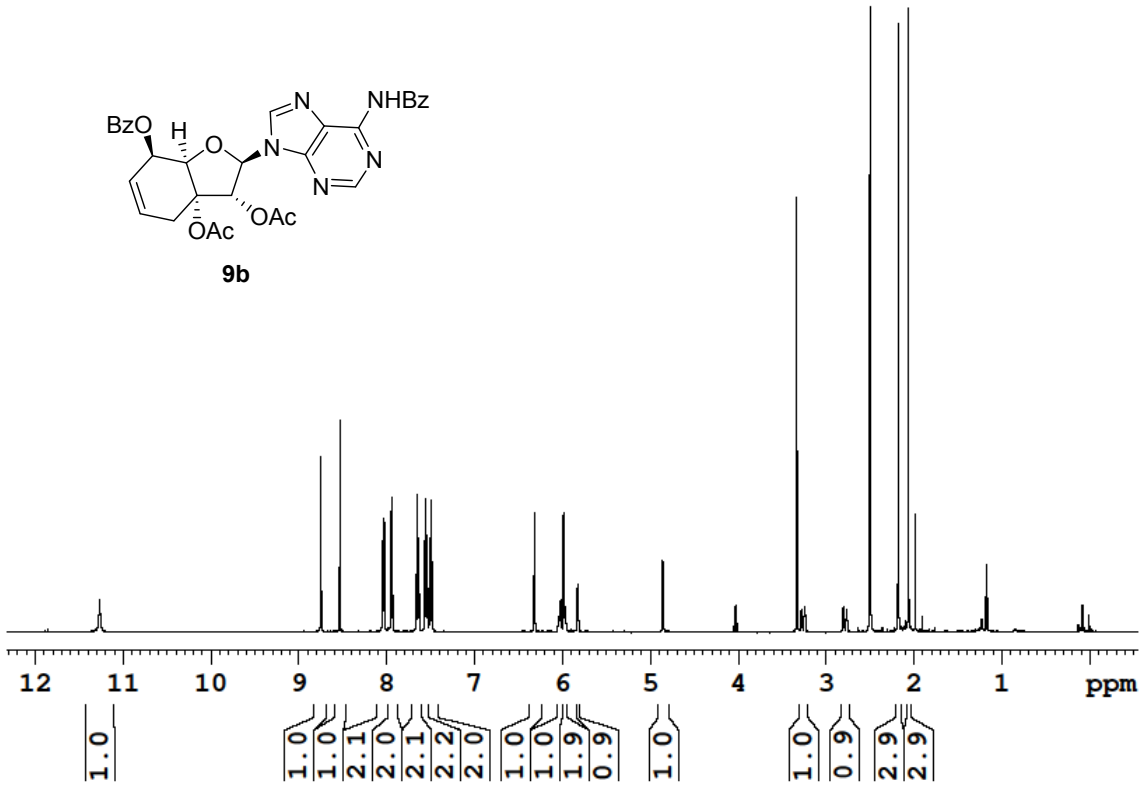
8b

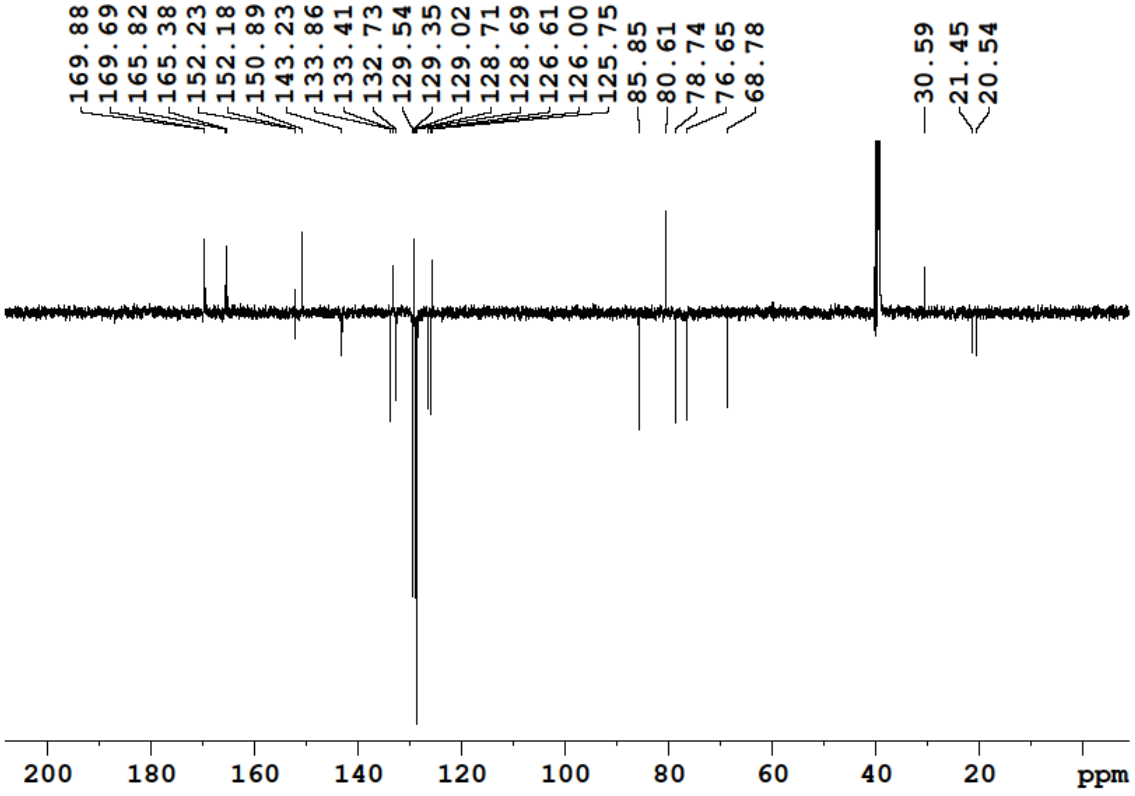

165.13
133.63
130.05
129.34
129.01
128.85
127.99
111.71
103.25
84.13
80.59
78.57
69.63
32.03
26.82
26.68
26.62
200
180
160
140
120
100
80
60
40
20
0
ppm

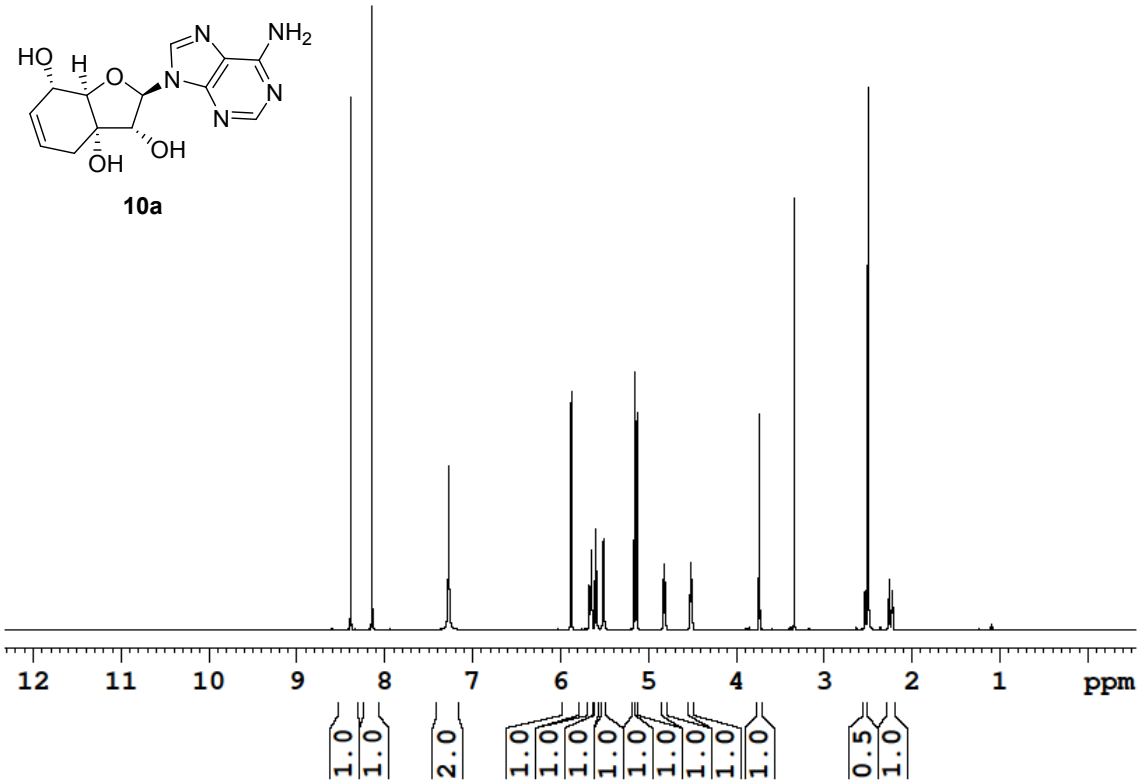

BzO
H
O
N
N
N
N
NHBz
OAc
OAc
9a
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.0
2.0
2.1
2.0
2.1
4.1
1.0
1.0
2.0
1.0
1.0
1.9
3.1
3.1
170.04
169.74
165.85
165.18
152.13
150.90
144.35
133.85
133.46
132.73
129.53
129.46
129.02
128.72
128.69
128.05
126.18
124.23
86.09
85.92
81.51
80.83
74.91
70.96
30.12
21.67
20.55
200
180
160
140
120
100
80
60
40
20
ppm

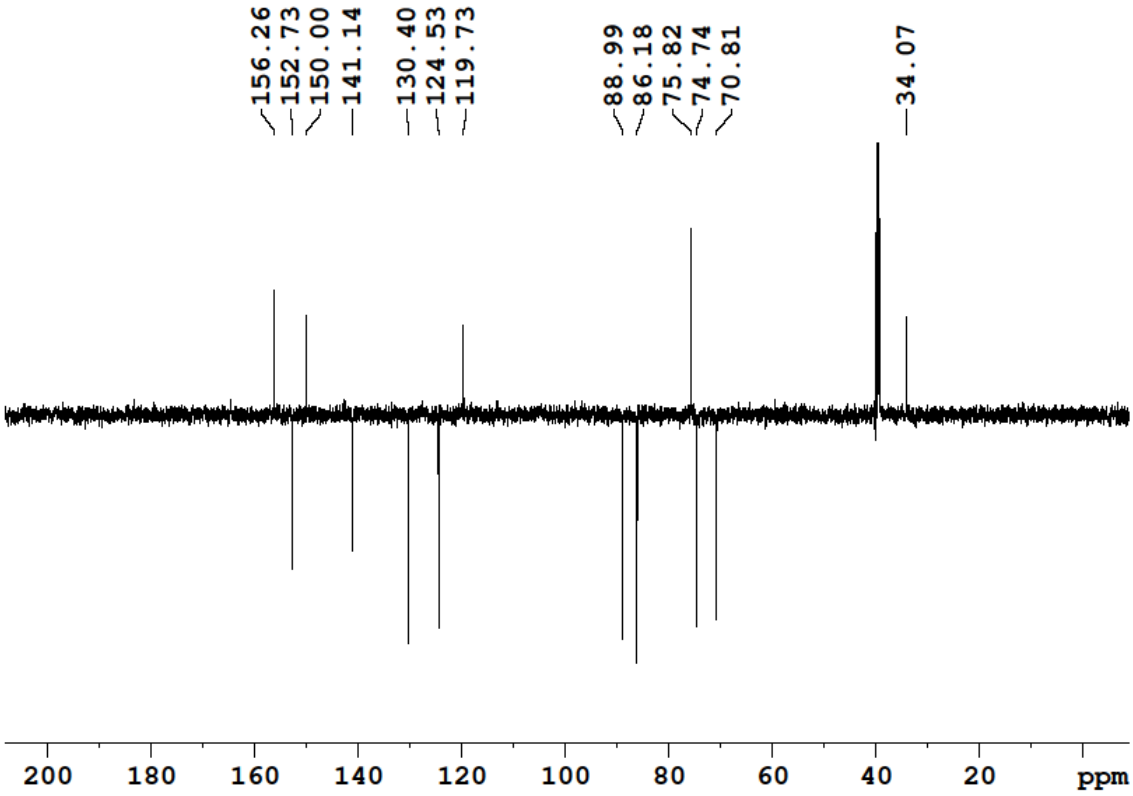
BzO
H
O
N
N
N
N
NHBz
OAc
OAc

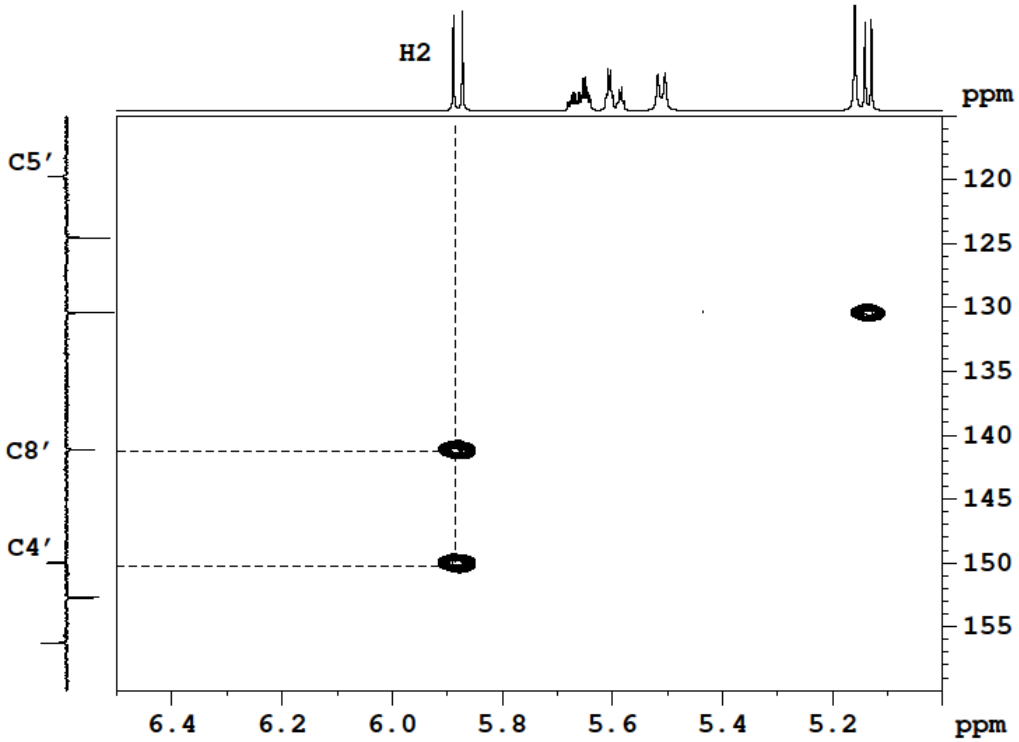
9b

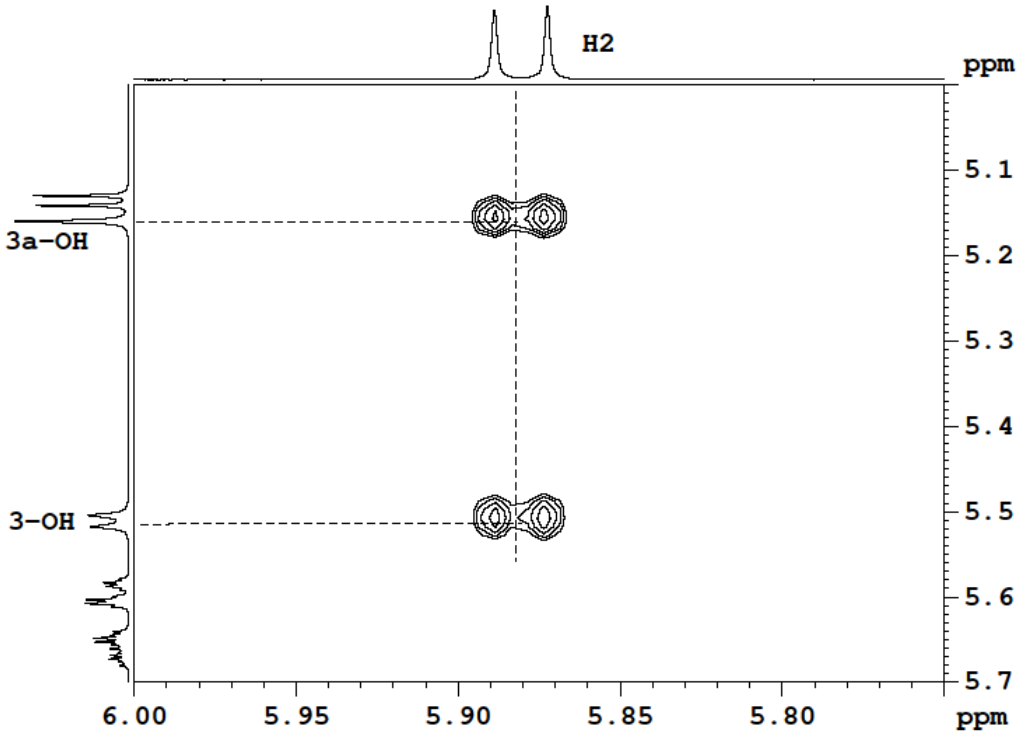

12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
1.0
2.1
2.0
2.1
2.2
2.0
1.0
1.0
1.9
0.9
1.0
1.0
0.9
2.9
2.9

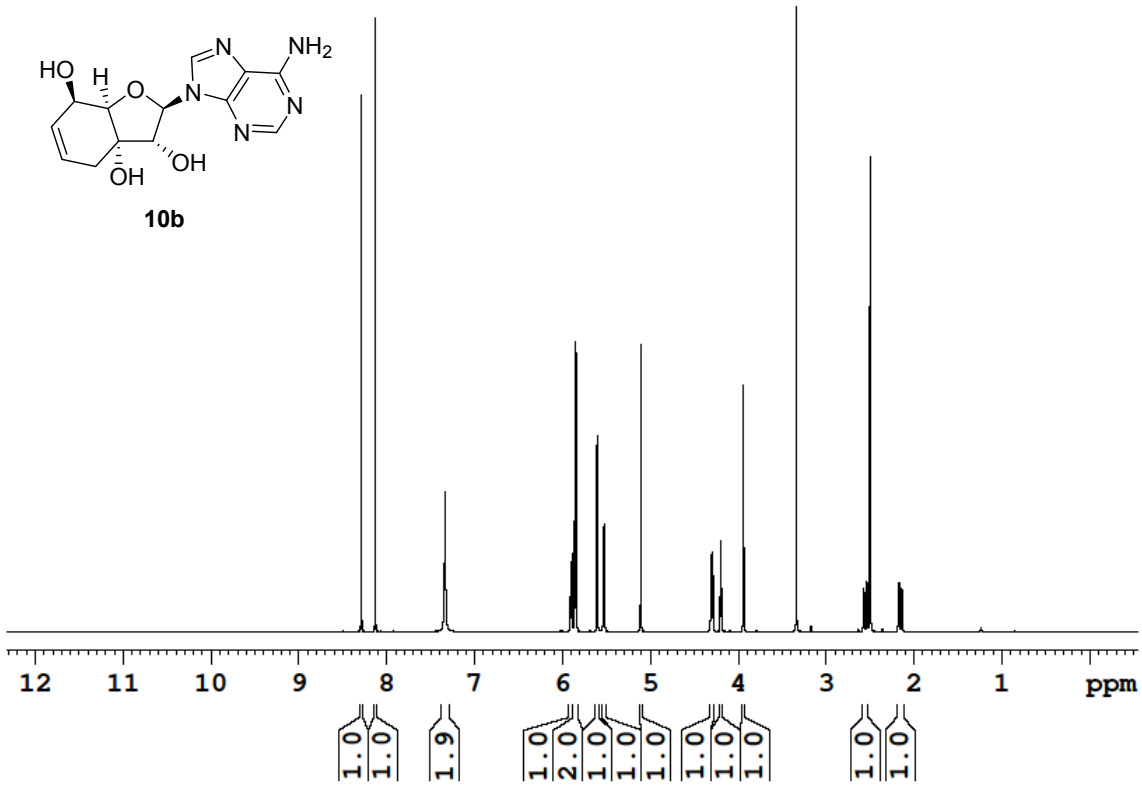

169.88
169.69
165.82
165.38
152.23
152.18
150.89
143.23
133.86
133.41
132.73
129.54
129.35
129.02
128.71
128.69
126.61
126.00
125.75
85.85
80.61
78.74
76.65
68.78
30.59
21.45
20.54
200
180
160
140
120
100
80
60
40
20
ppm


HO
H
O
N
N
N
N
NH2
OH
OH
10a
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
2.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
0.5
1.0

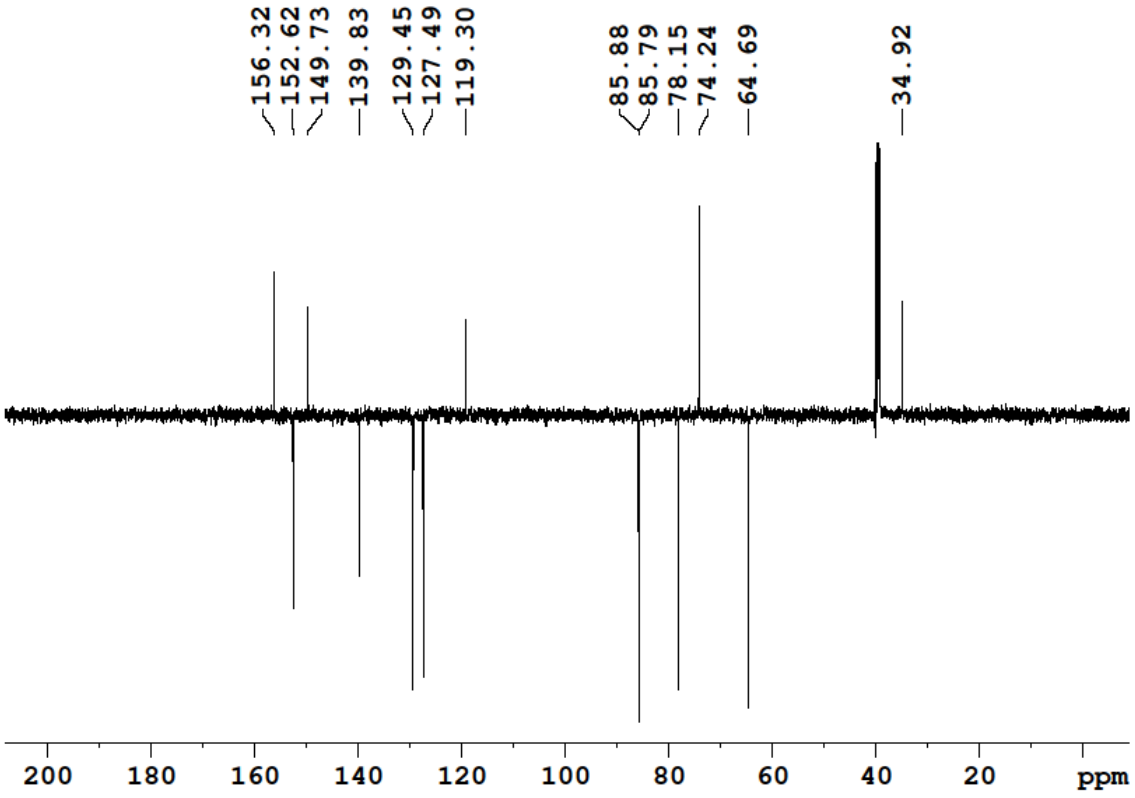

156.26
152.73
150.00
141.14
130.40
124.53
119.73
88.99
86.18
75.82
74.74
70.81
34.07
200
180
160
140
120
100
80
60
40
20
ppm

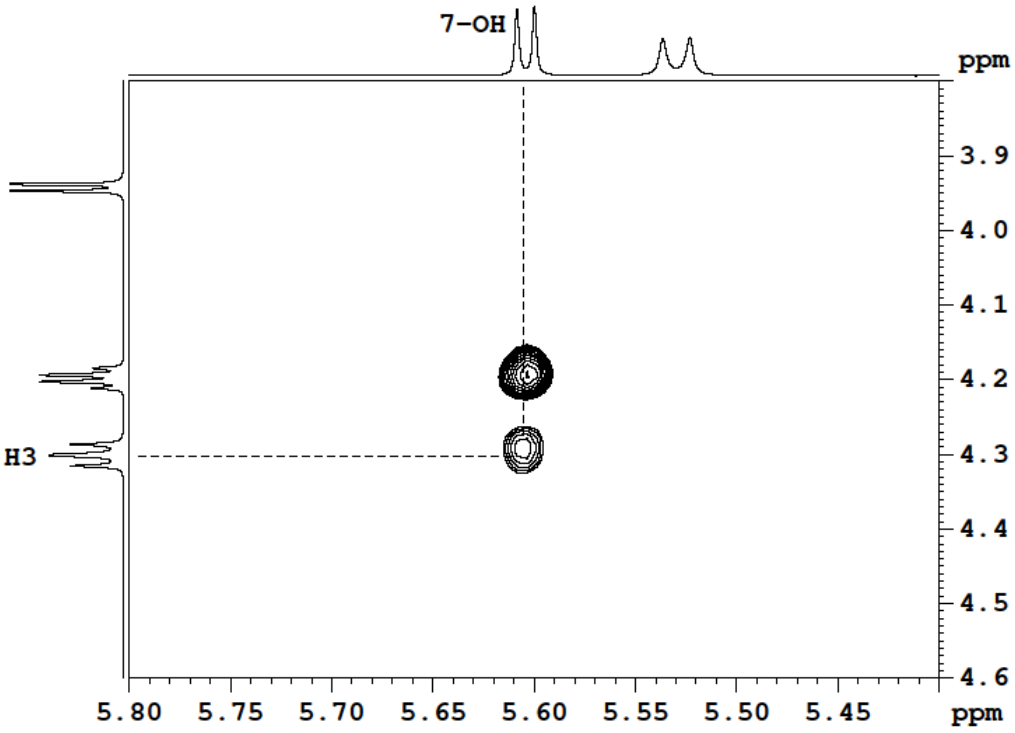

H2
ppm
C5′
C8′
C4′
120
125
130
135
140
145
150
155
6.4
6.2
6.0
5.8
5.6
5.4
5.2
ppm

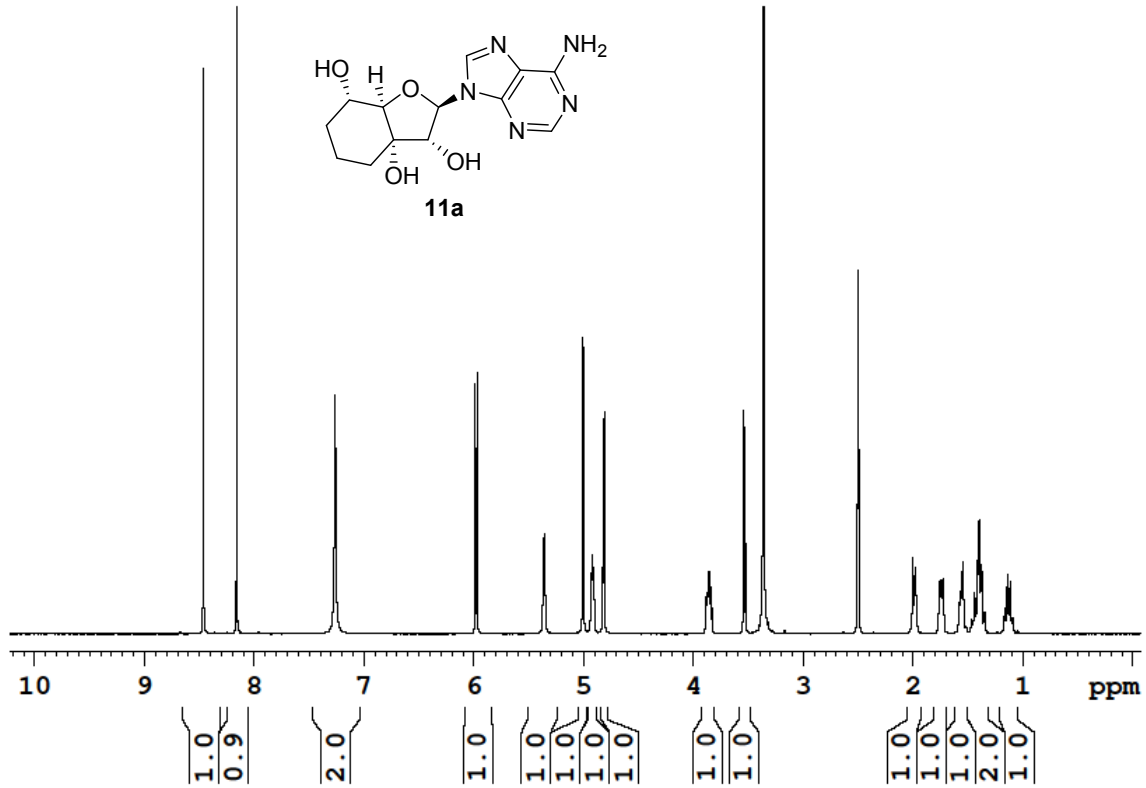

H2
ppm
3a-OH
3-OH
5.1
5.2
5.3
5.4
5.5
5.6
5.7
6.00
5.95
5.90
5.85
5.80
ppm

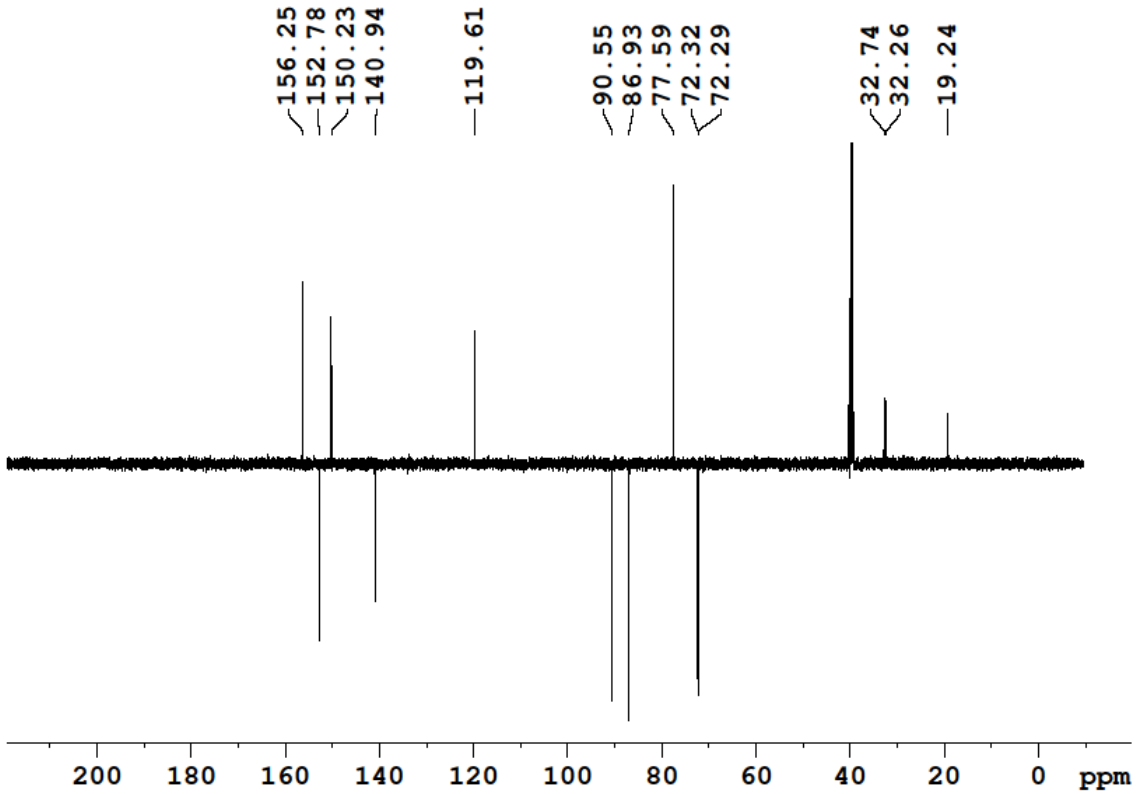

HO
H
O
N
N
N
N
NH2
OH
OH
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
1.9
1.0
2.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0

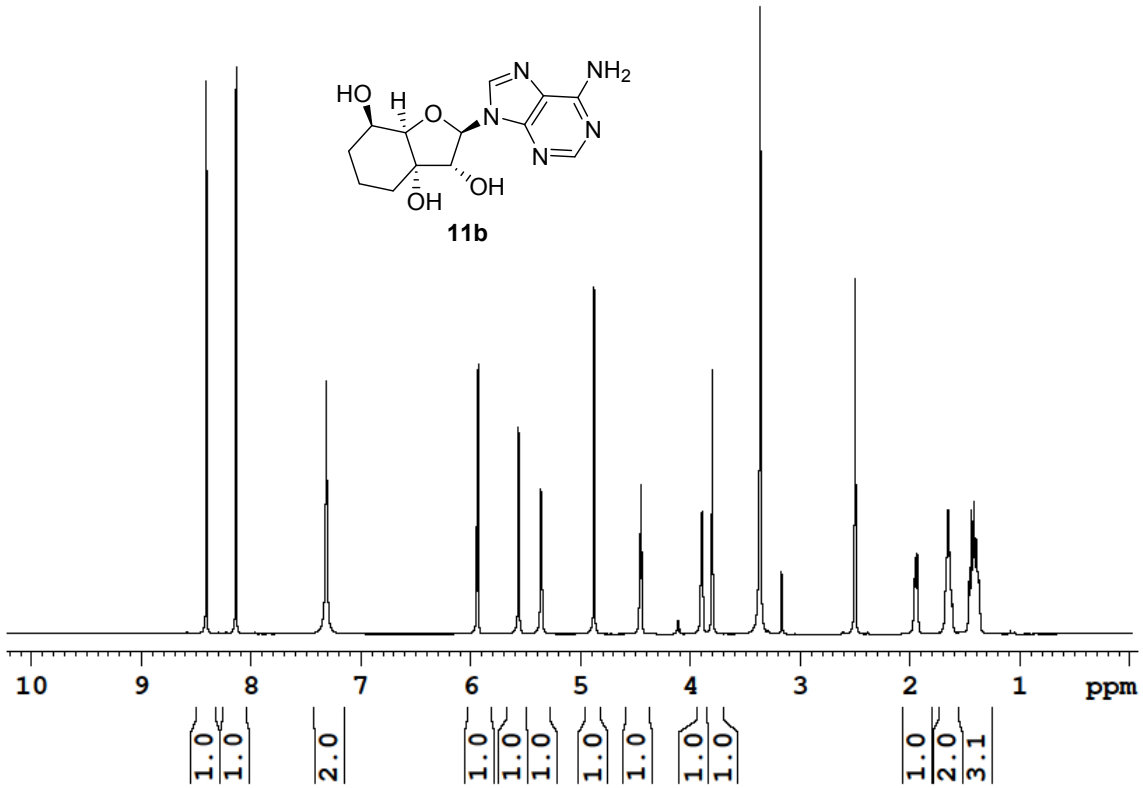
10b

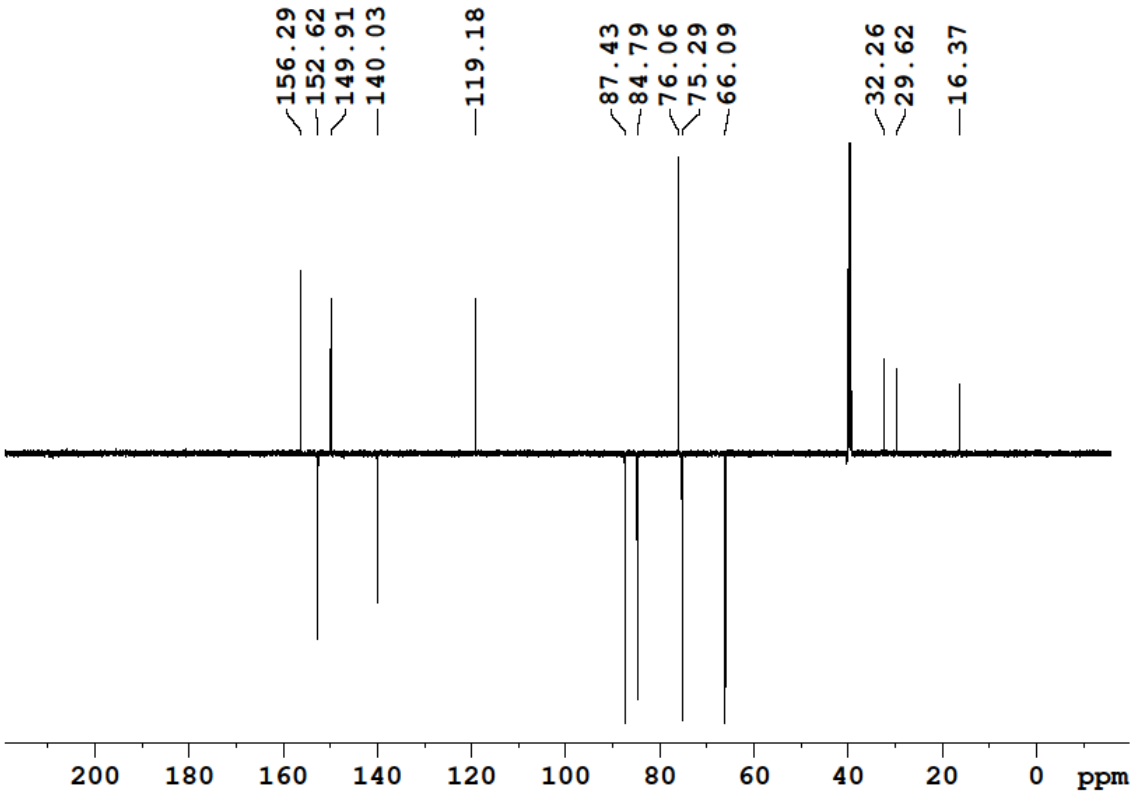

156.32
152.62
149.73
139.83
129.45
127.49
119.30
85.88
85.79
78.15
74.24
64.69
34.92
200
180
160
140
120
100
80
60
40
20
ppm


7-OH
ppm
3.9
4.0
4.1
4.2
4.3
4.4
4.5
4.6
H3
5.80
5.75
5.70
5.65
5.60
5.55
5.50
5.45
ppm


HO
H
O
N
N
N
N
NH2
OH
OH
11a
10
9
8
7
6
5
4
3
2
1
ppm
1.0
0.9
2.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
2.0
1.0

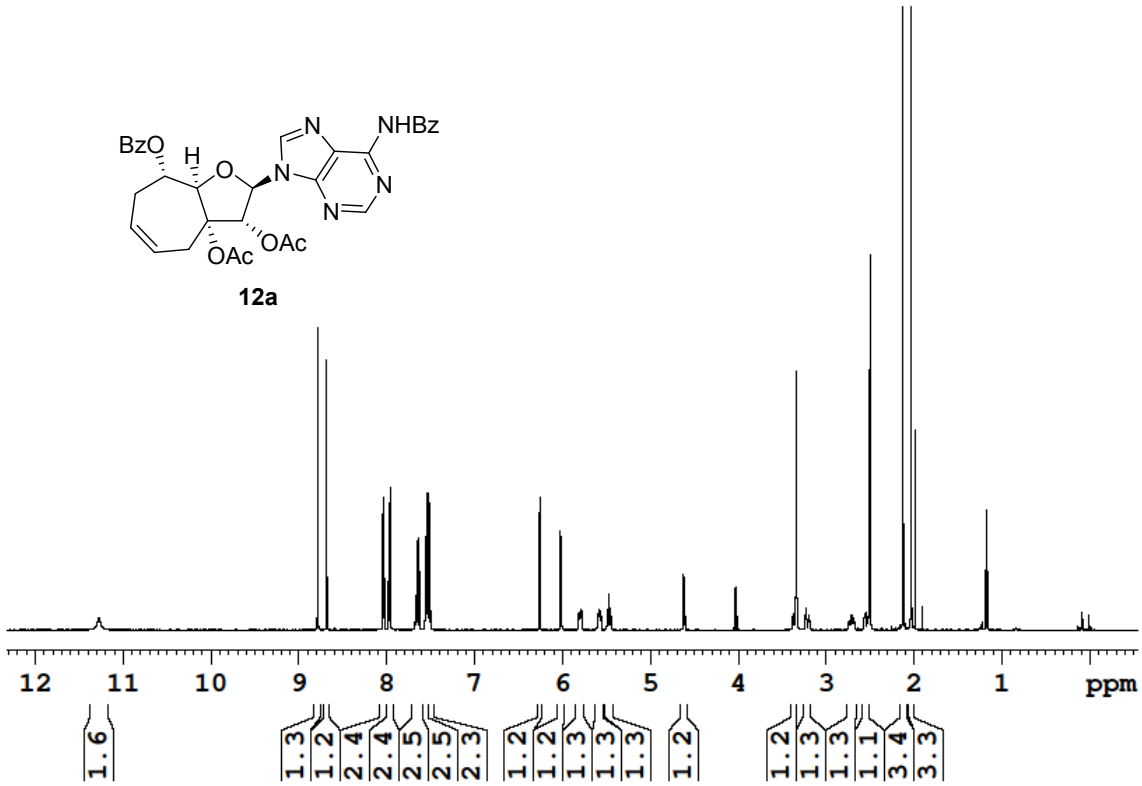

156.25
152.78
150.23
140.94
119.61
90.55
86.93
77.59
72.32
72.29
32.74
32.26
19.24
200
180
160
140
120
100
80
60
40
20
0
ppm

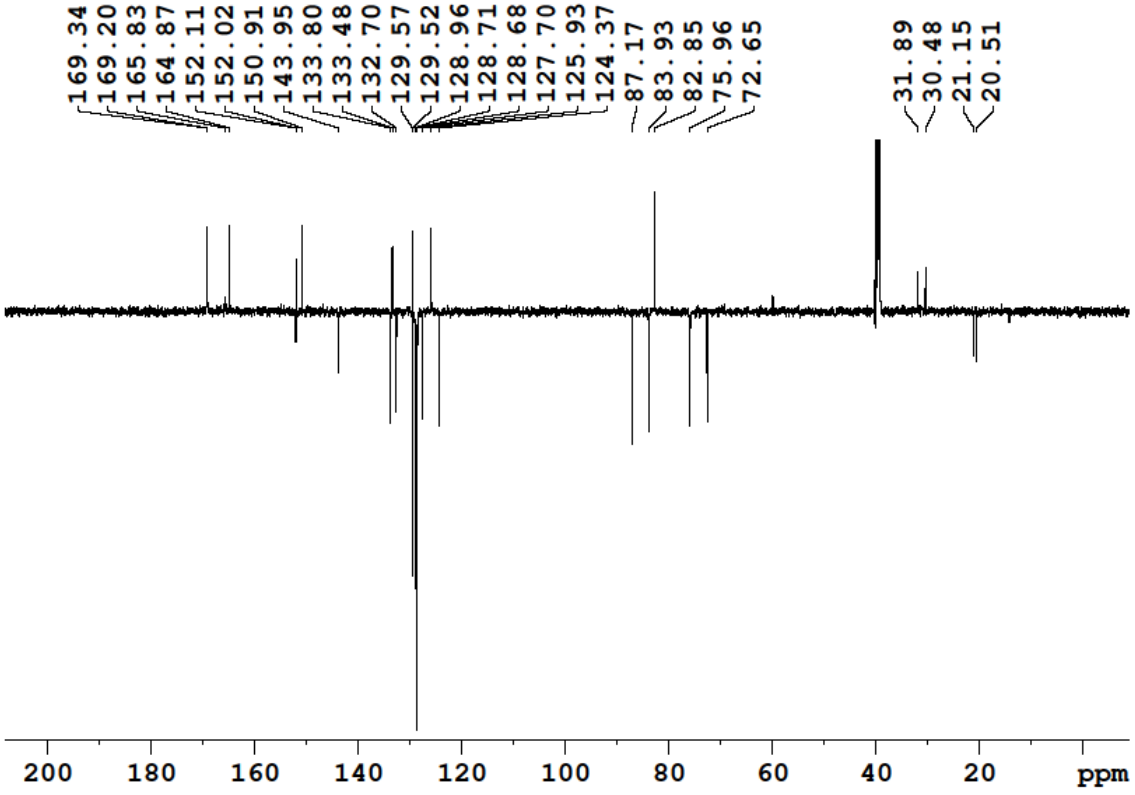

HO
H
O
N
N
N
N
NH2
OH
OH
11b
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
2.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
2.0
3.1

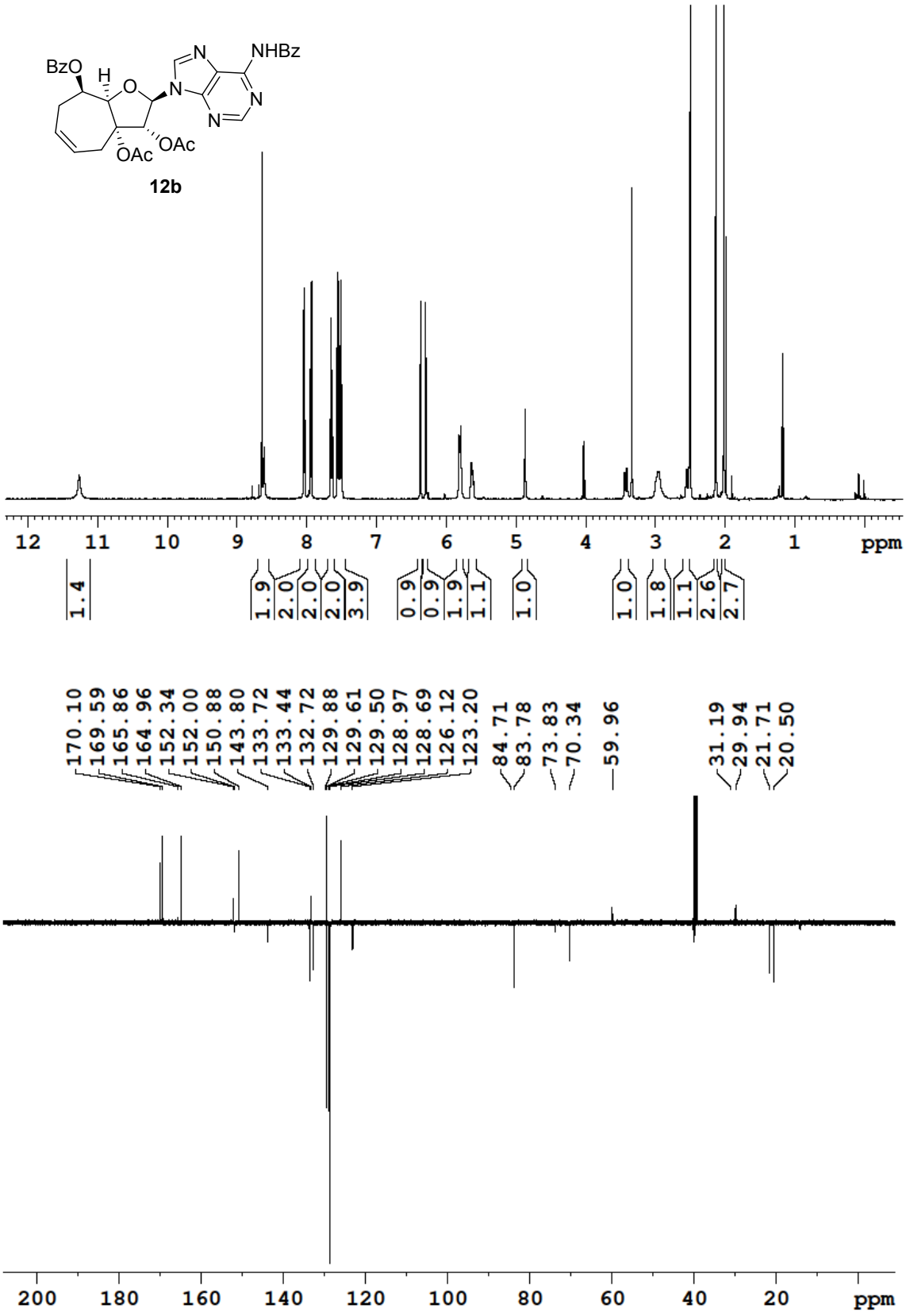

156.29
152.62
149.91
140.03
119.18
87.43
84.79
76.06
75.29
66.09
32.26
29.62
16.37
200
180
160
140
120
100
80
60
40
20
0
ppm

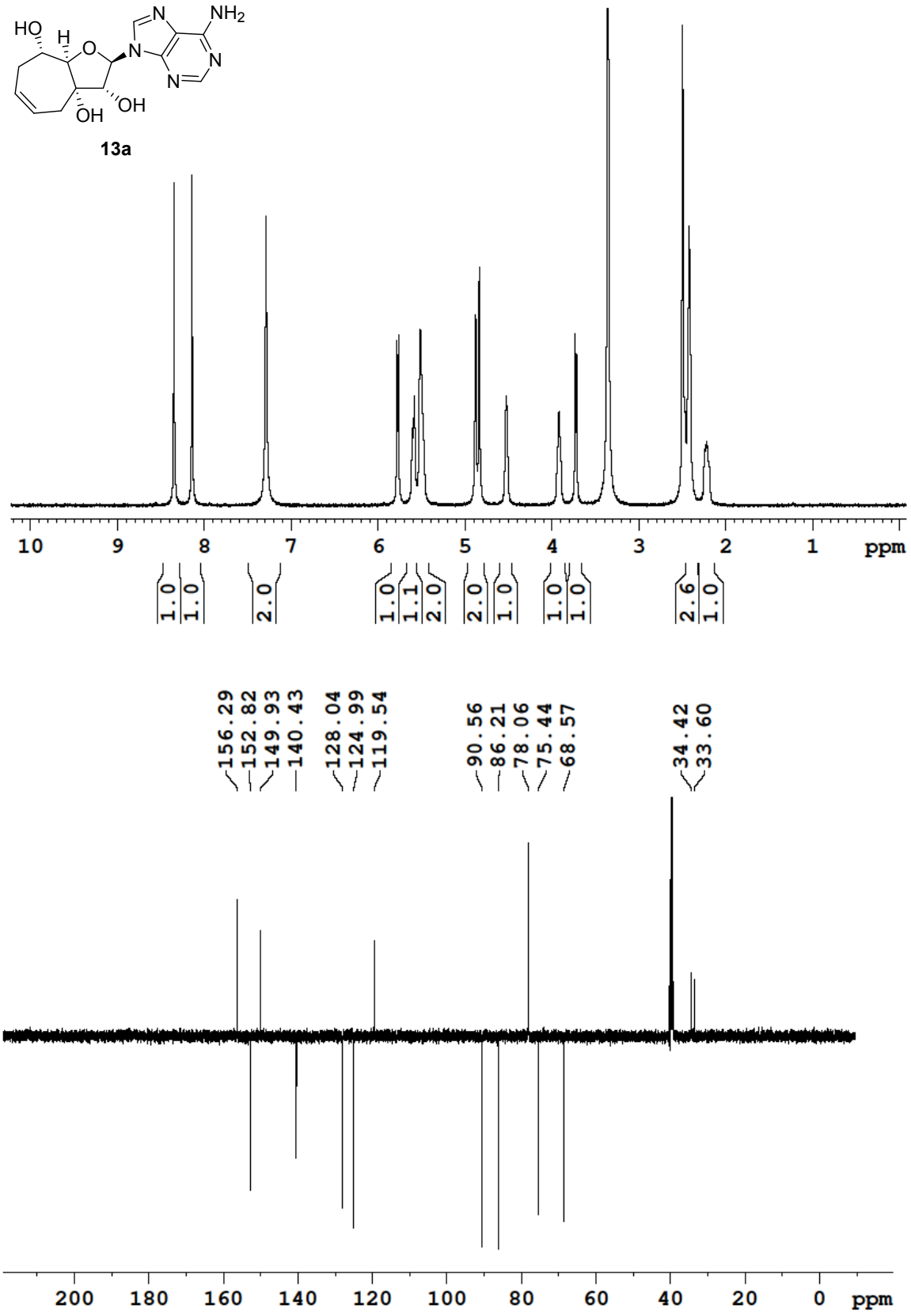
BzO
H
O
N
N
N
N
NHBz
OAc
OAc

12a


12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.6
1.3
1.2
2.4
2.4
2.5
2.5
2.3
1.2
1.2
1.3
1.3
1.3
1.2
1.2
1.3
1.3
1.1
3.4
3.3

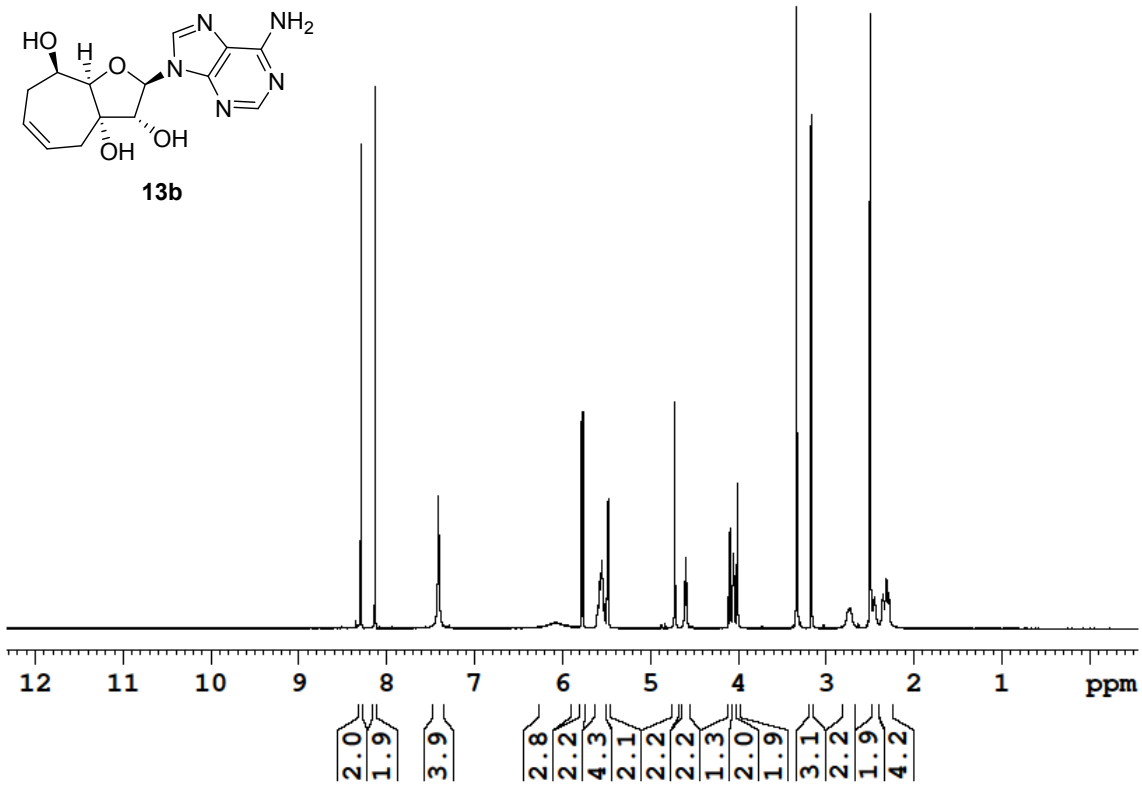

169.34
169.20
165.83
164.87
152.11
152.02
150.91
143.95
133.80
133.48
132.70
129.57
129.52
128.96
128.71
128.68
127.70
125.93
124.37
87.17
83.93
82.85
75.96
72.65
31.89
30.48
21.15
20.51
200
180
160
140
120
100
80
60
40
20
ppm

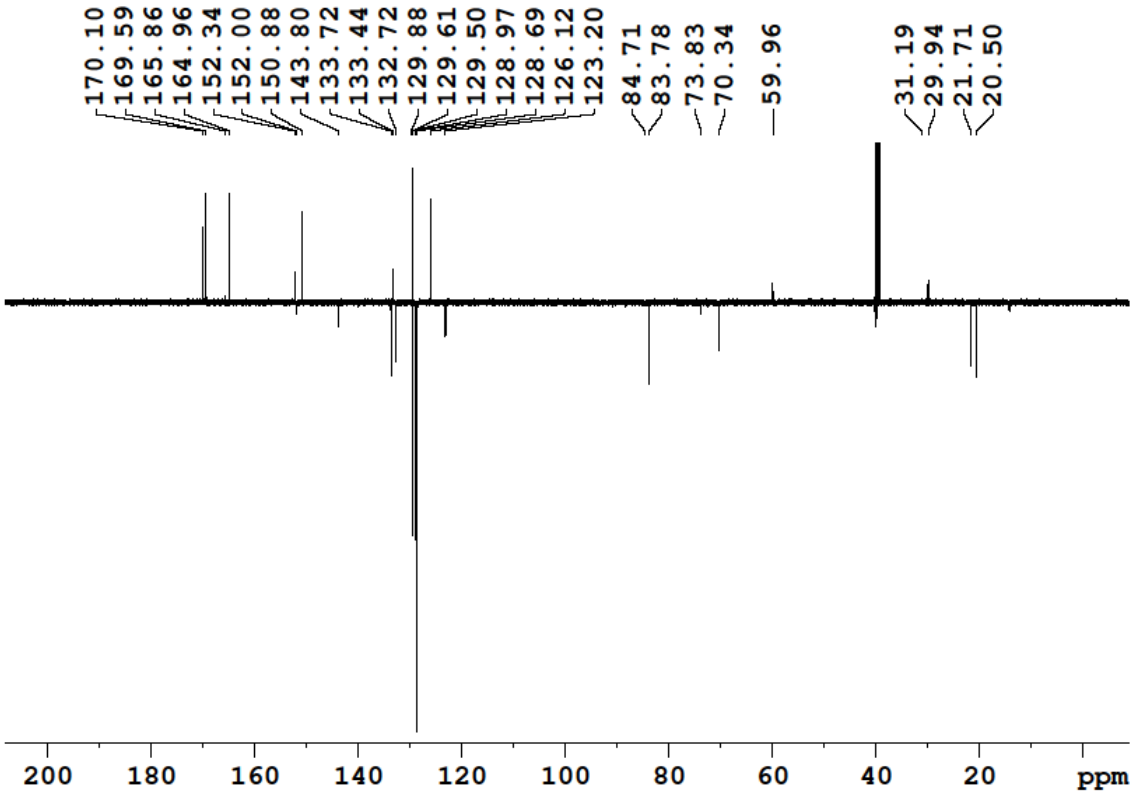

BzO
H
O
N
N
N
N
NHBz
OAc
OAc
12b
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.4
1.9
2.0
2.0
2.0
3.9
0.9
0.9
1.9
1.1
1.0
1.0
1.8
1.1
2.6
2.7
170.10
169.59
165.86
164.96
152.34
152.00
150.88
143.80
133.72
133.44
132.72
129.88
129.61
129.50
128.97
128.69
126.12
123.20
84.71
83.78
73.83
70.34
59.96
31.19
29.94
21.71
20.50
200
180
160
140
120
100
80
60
40
20
ppm

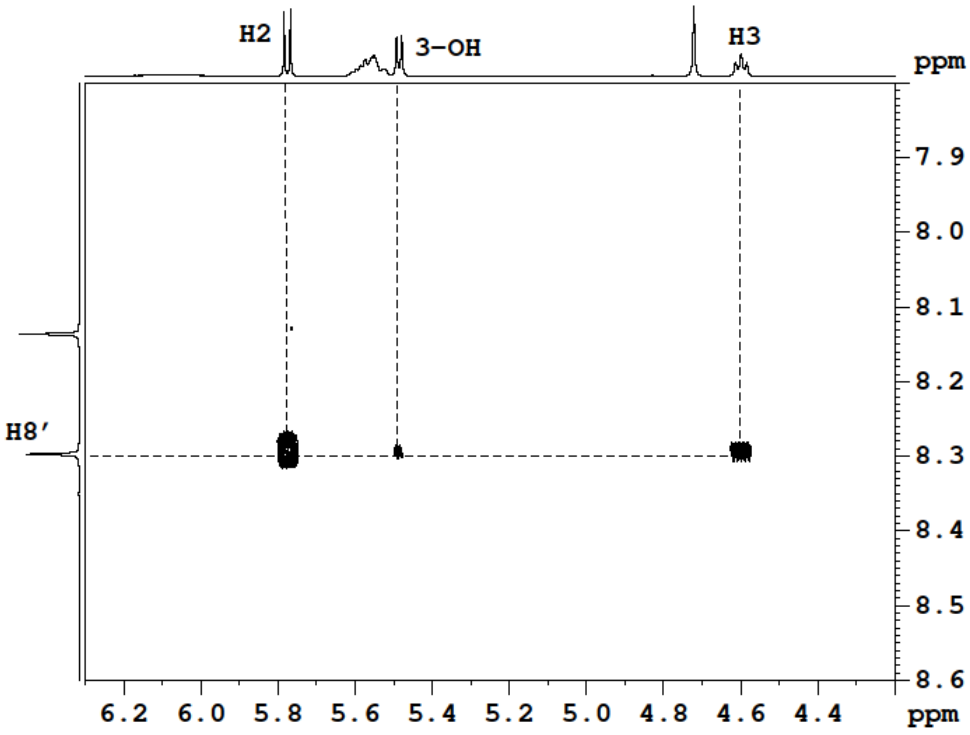

HO
H
O
N
N
N
N
NH2
OH
OH
13a
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
2.0
1.0
1.1
2.0
2.0
1.0
1.0
1.0
2.6
1.0
156.29
152.82
149.93
140.43
128.04
124.99
119.54
90.56
86.21
78.06
75.44
68.57
34.42
33.60
200
180
160
140
120
100
80
60
40
20
0
ppm

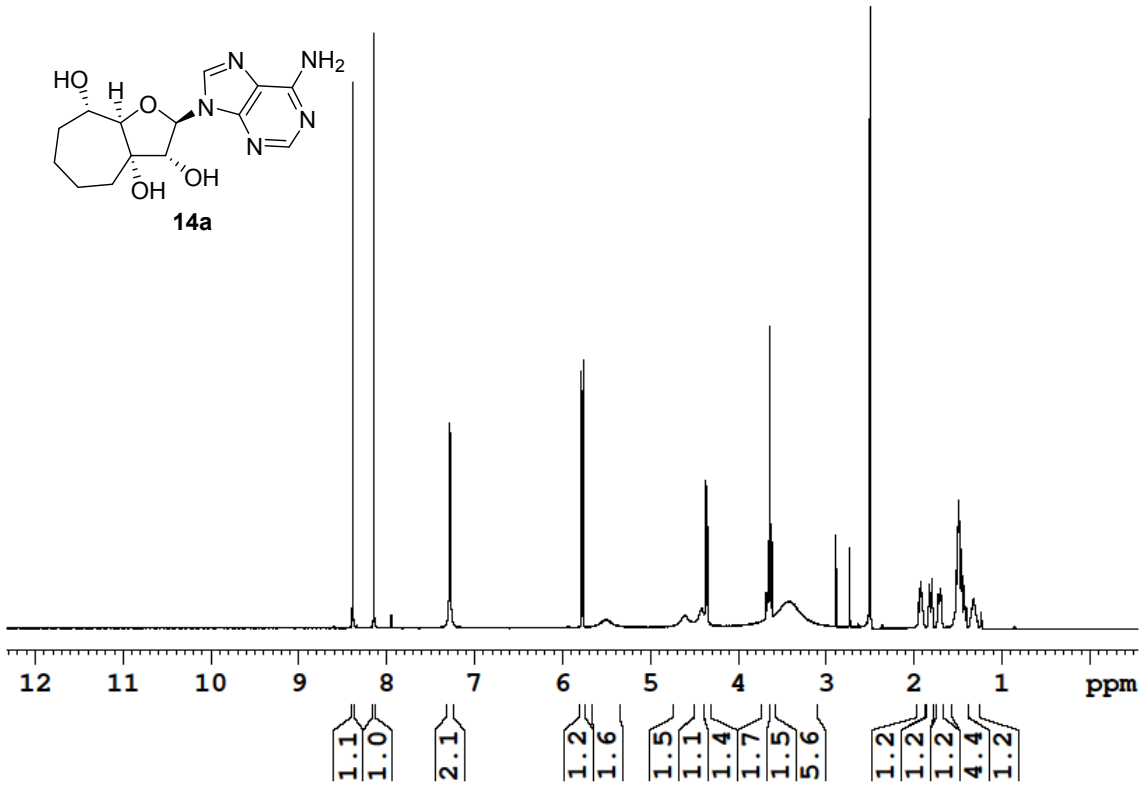
HO
H
O
N
N
N
N
NH2
OH
OH

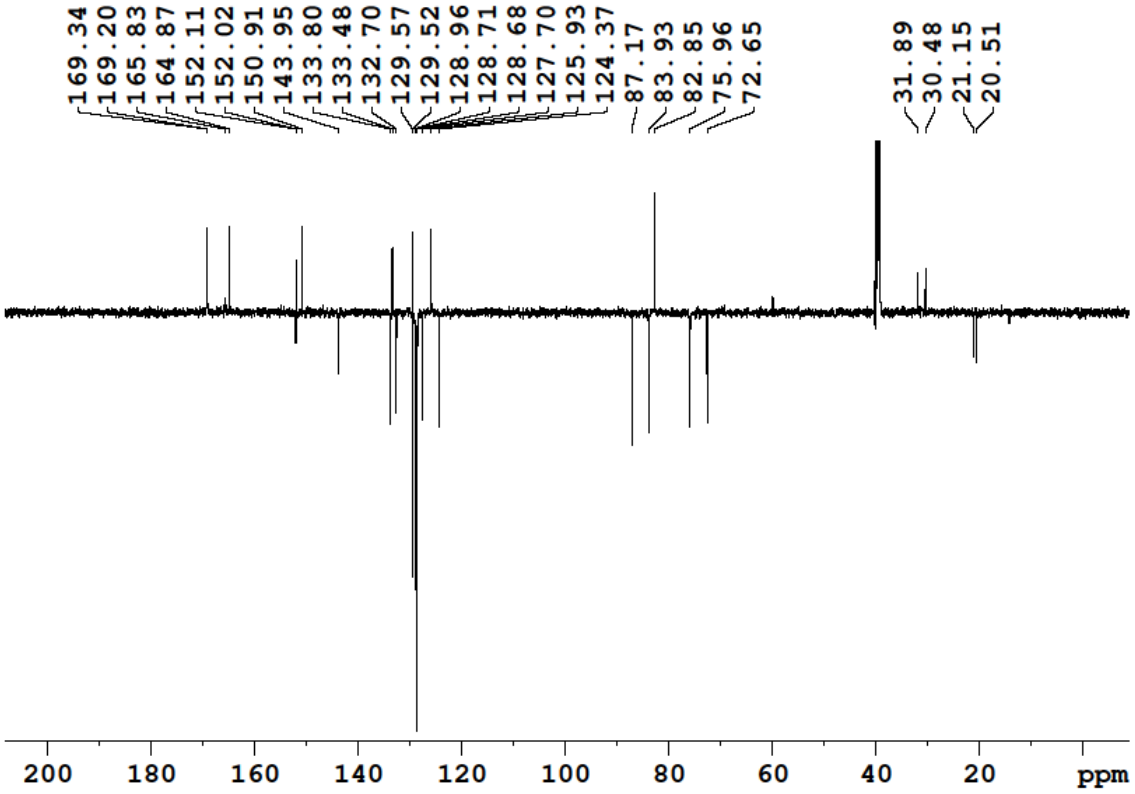
13b

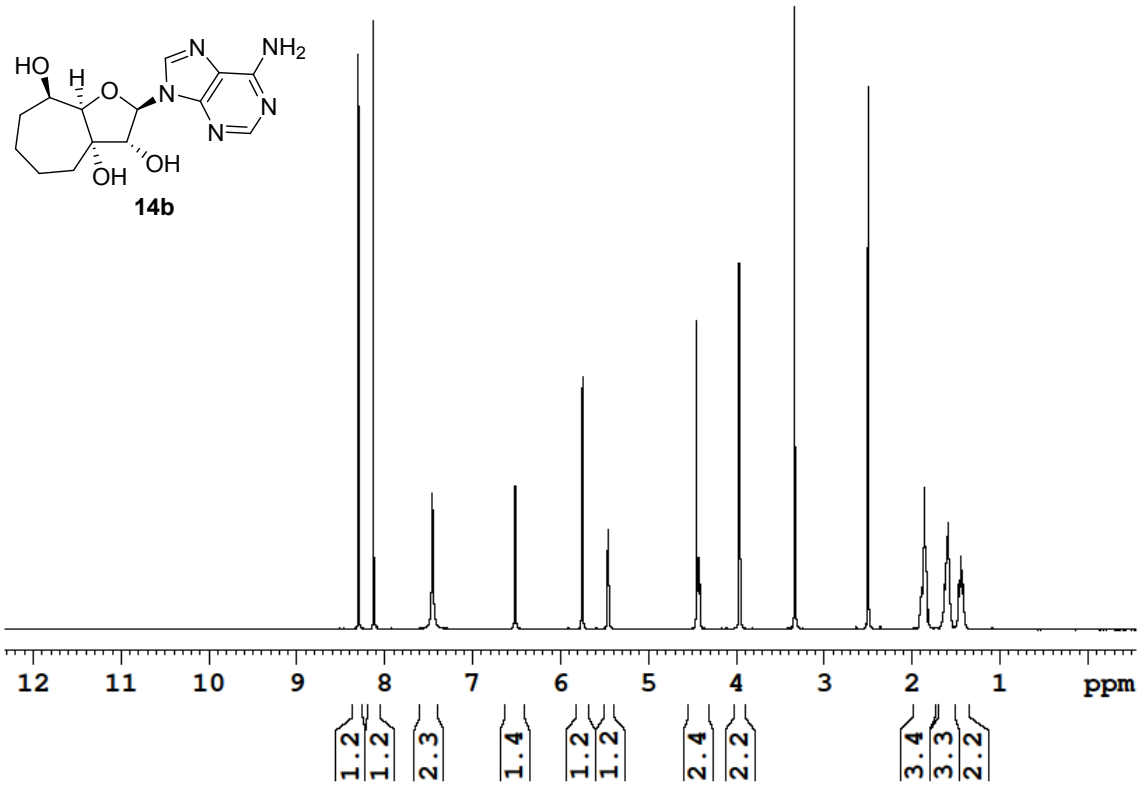

12
11
10
9
8
7
6
5
4
3
2
1
ppm
2.0
1.9
3.9
2.8
2.2
4.3
2.1
2.2
2.2
1.3
2.0
1.9
3.1
2.2
1.9
4.2

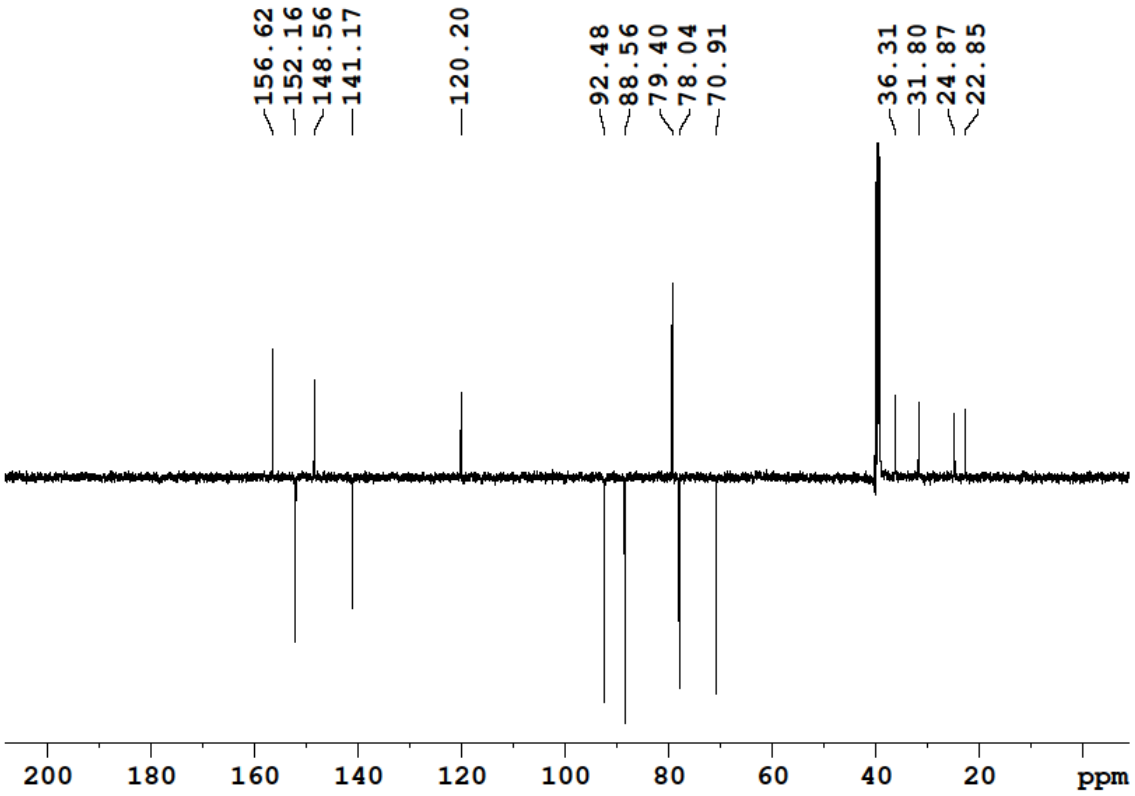

170.10
169.59
165.86
164.96
152.34
152.00
150.88
143.80
133.72
133.44
132.72
129.88
129.61
129.50
128.97
128.69
126.12
123.20
84.71
83.78
73.83
70.34
59.96
31.19
29.94
21.71
20.50
200
180
160
140
120
100
80
60
40
20
ppm

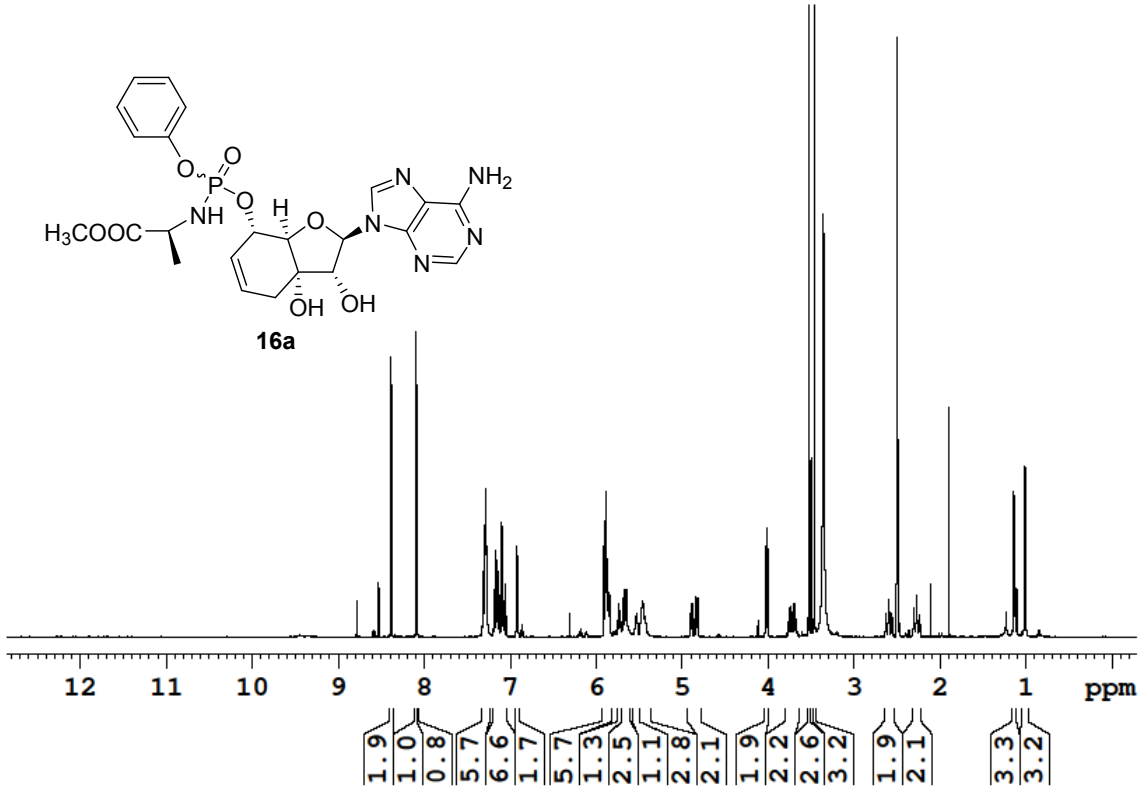

H2
3-OH
H3
ppm
7.9
8.0
8.1
8.2
8.3
8.4
8.5
8.6
H8′
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
ppm

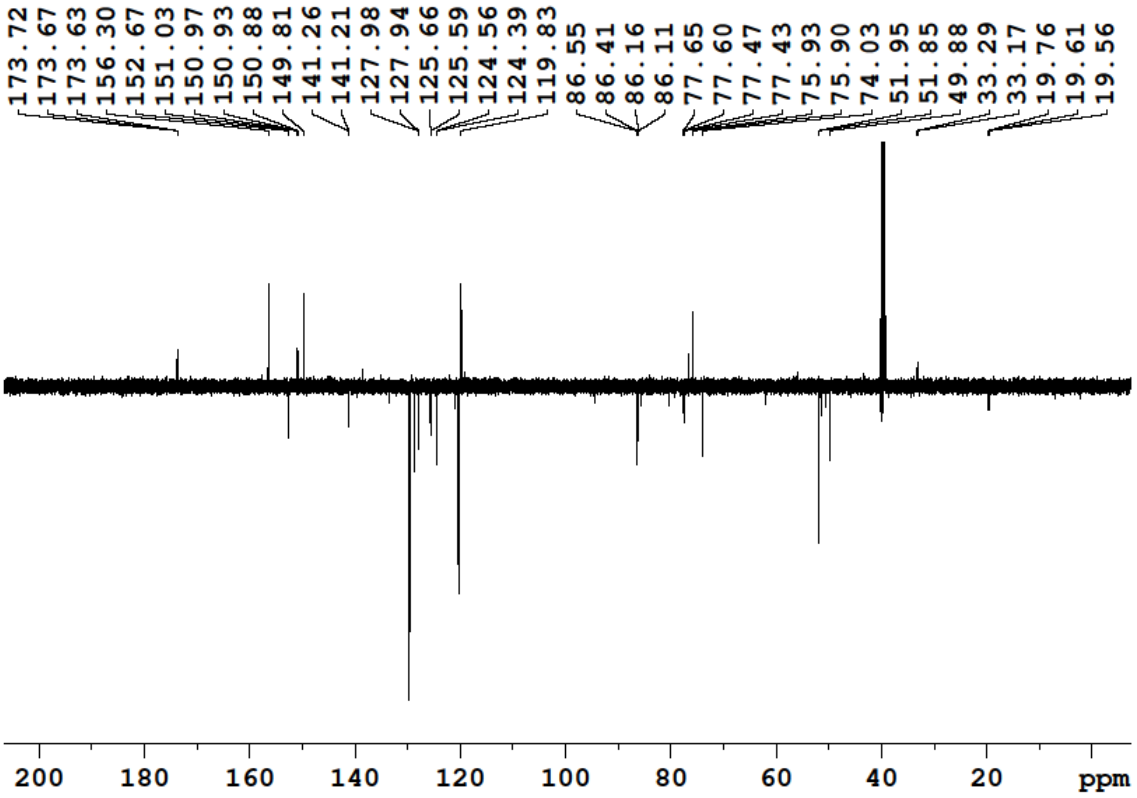

HO
H
O
N
N
N
N
NH2
OH
OH
14a
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.1
1.0
2.1
1.2
1.6
1.5
1.1
1.4
1.7
1.5
5.6
1.2
1.2
1.2
4.4
1.2

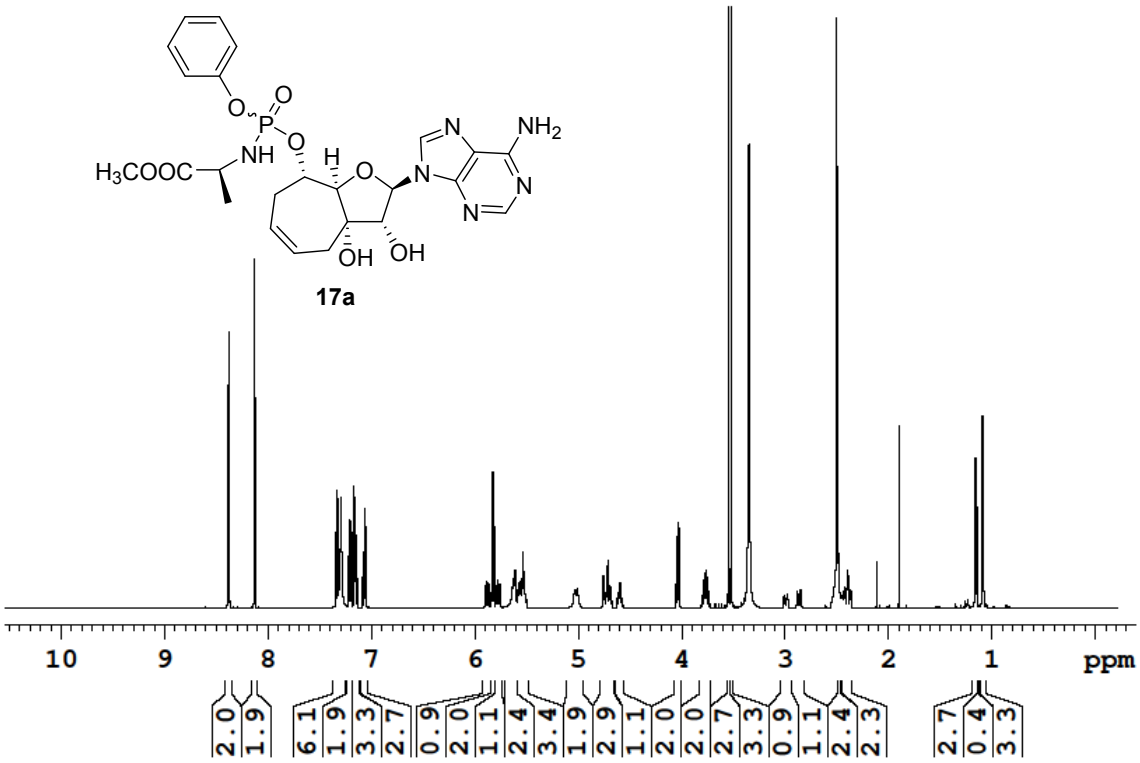

169.34
169.20
165.83
164.87
152.11
152.02
150.91
143.95
133.80
133.48
132.70
129.57
129.52
128.96
128.71
128.68
127.70
125.93
124.37
87.17
83.93
82.85
75.96
72.65
31.89
30.48
21.15
20.51
200
180
160
140
120
100
80
60
40
20
ppm

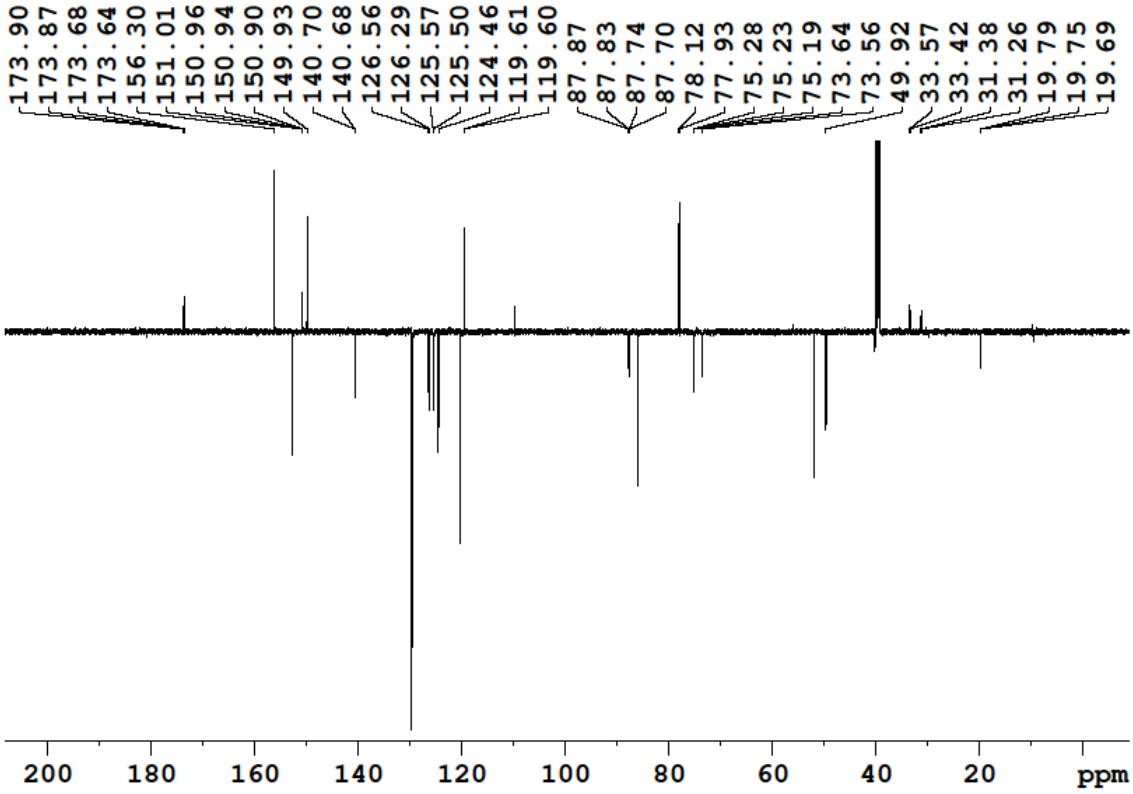

HO
H
O
N
N
N
N
NH2
OH
OH
14b
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.2
1.2
2.3
1.4
1.2
1.2
2.4
2.2
3.4
3.3
2.2

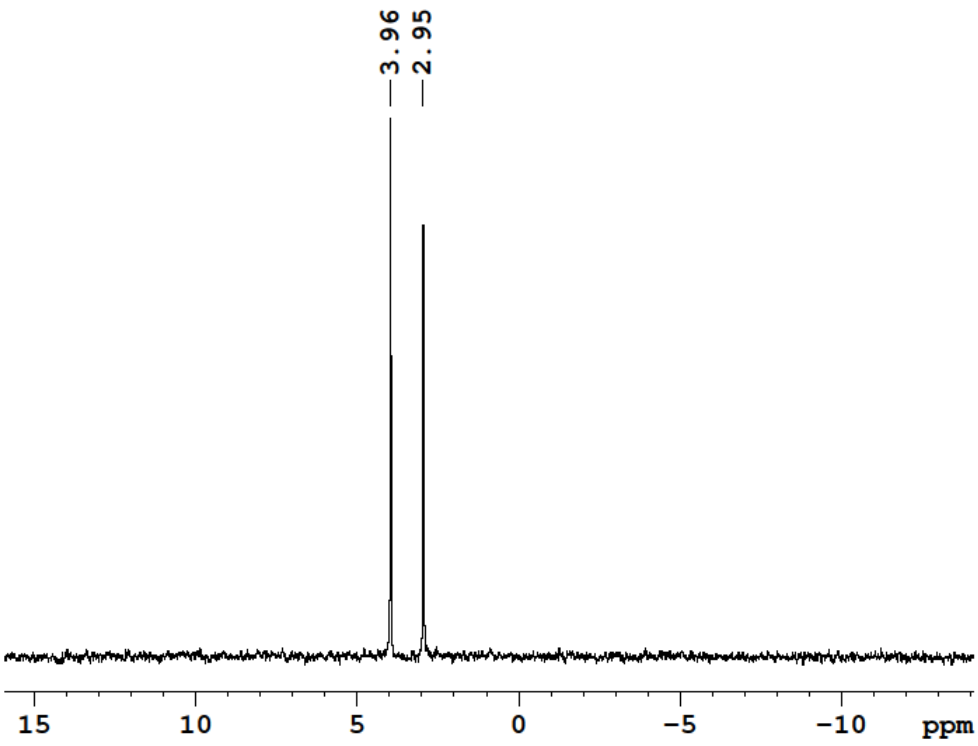

156.62
152.16
148.56
141.17
120.20
92.48
88.56
79.40
78.04
70.91
36.31
31.80
24.87
22.85
200
180
160
140
120
100
80
60
40
20
ppm

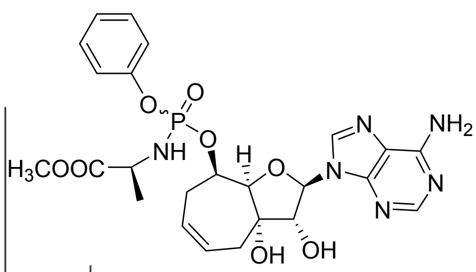

16a
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.9
1.0
0.8
5.7
6.6
1.7
5.7
1.3
2.5
1.1
2.8
2.1
1.9
2.2
2.6
3.2
1.9
2.1
3.3
3.2


173.72
173.67
173.63
156.30
152.67
151.03
150.97
150.93
150.88
149.81
141.26
141.21
127.98
127.94
125.66
125.59
124.56
124.39
119.83
86.55
86.41
86.16
86.11
77.65
77.60
77.47
77.43
75.93
75.90
74.03
51.95
51.85
49.88
33.29
33.17
19.76
19.61
19.56
200
180
160
140
120
100
80
60
40
20
ppm

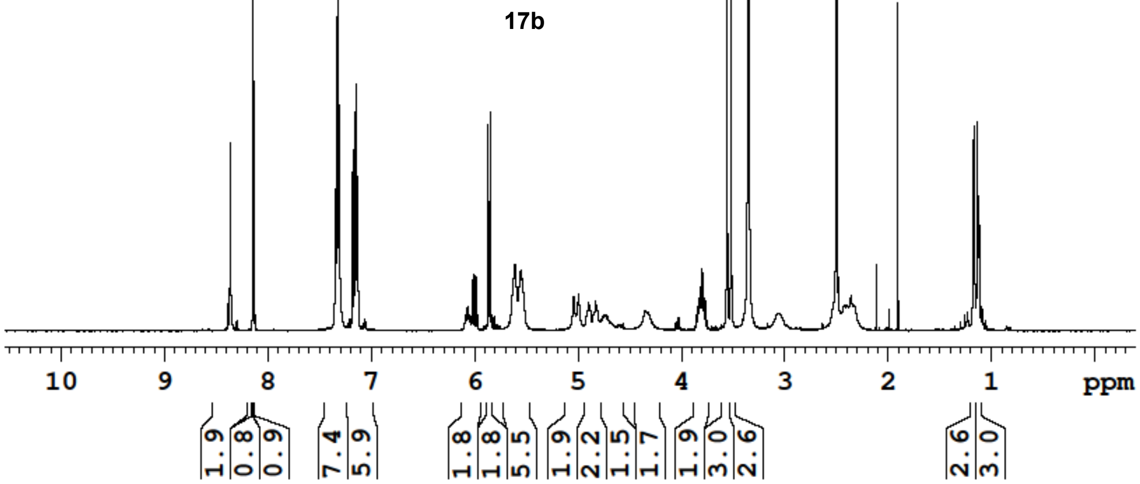

O
O
P
O
NH
H
O
N
NH2
H3COOC
N
N
N
OH
OH
17a
10
9
8
7
6
5
4
3
2
1
ppm
2.0
1.9
6.1
1.9
3.3
2.7
0.9
2.0
1.1
2.4
3.4
1.9
2.9
1.1
2.0
2.0
2.7
3.3
0.9
1.1
2.4
2.3
2.7
0.4
3.3

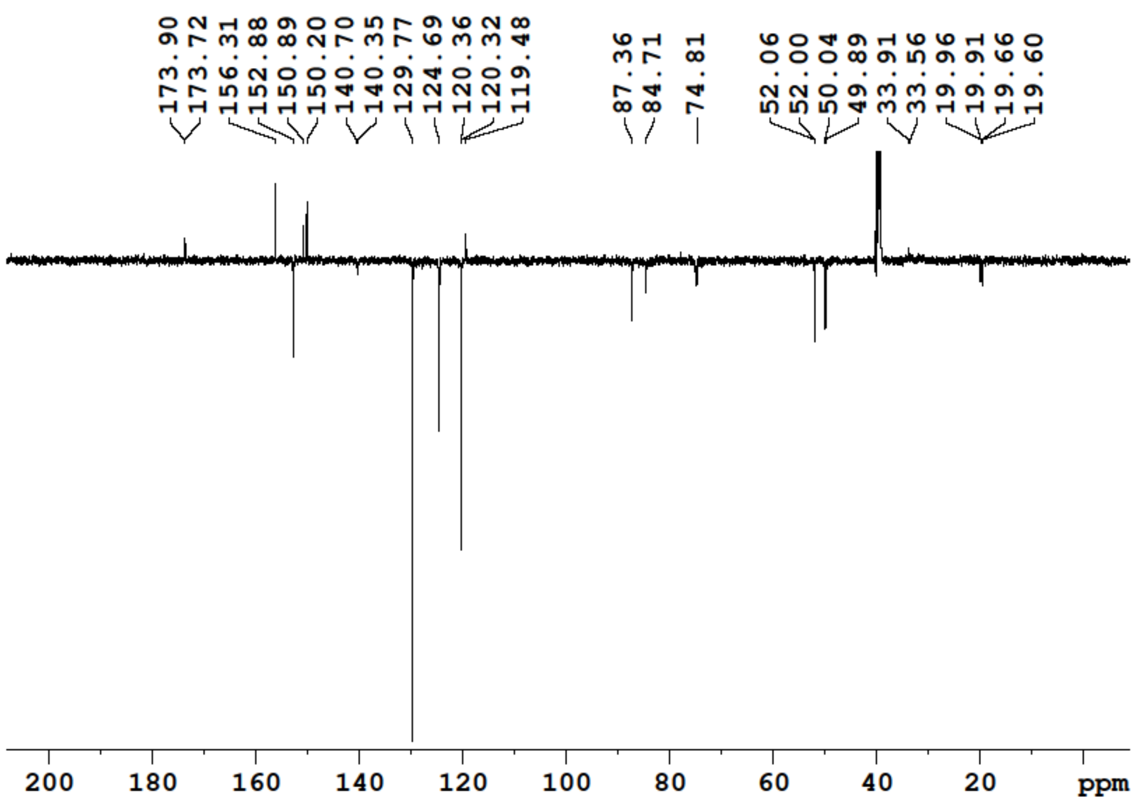

173.90
173.87
173.68
173.64
156.30
151.01
150.96
150.94
150.90
149.93
140.70
140.68
126.56
126.29
125.57
125.50
124.46
119.61
119.60
87.87
87.83
87.74
87.70
78.12
77.93
75.28
75.23
75.19
73.64
73.56
49.92
33.57
33.42
31.38
31.26
19.79
19.75
19.69
200
180
160
140
120
100
80
60
40
20
ppm

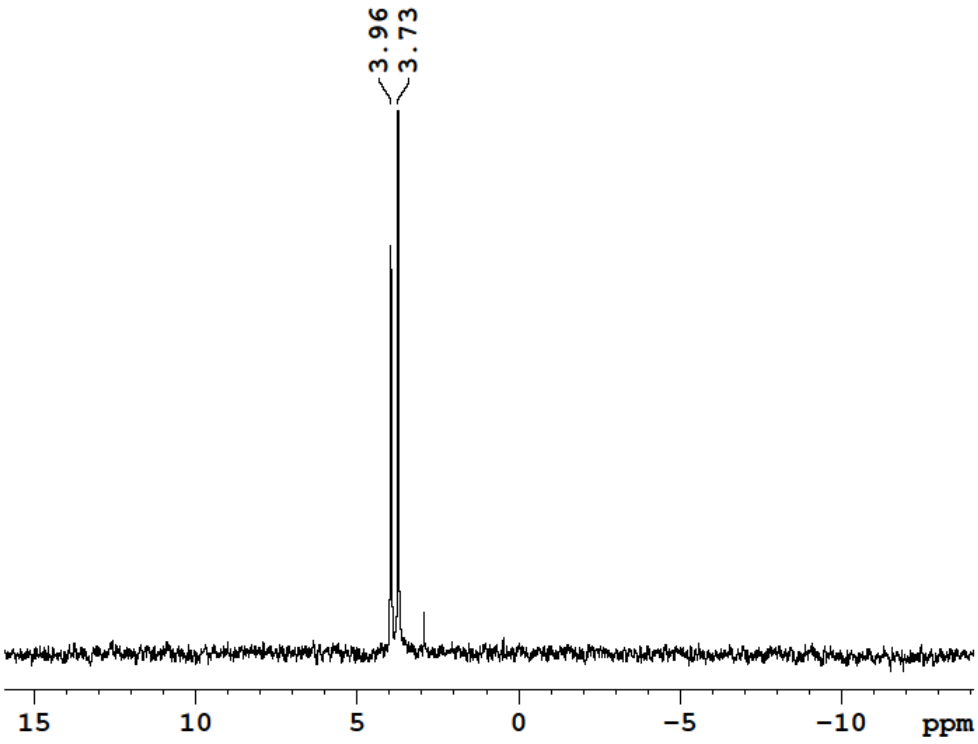

3.96
2.95
15
10
5
0
−5
−10
ppm

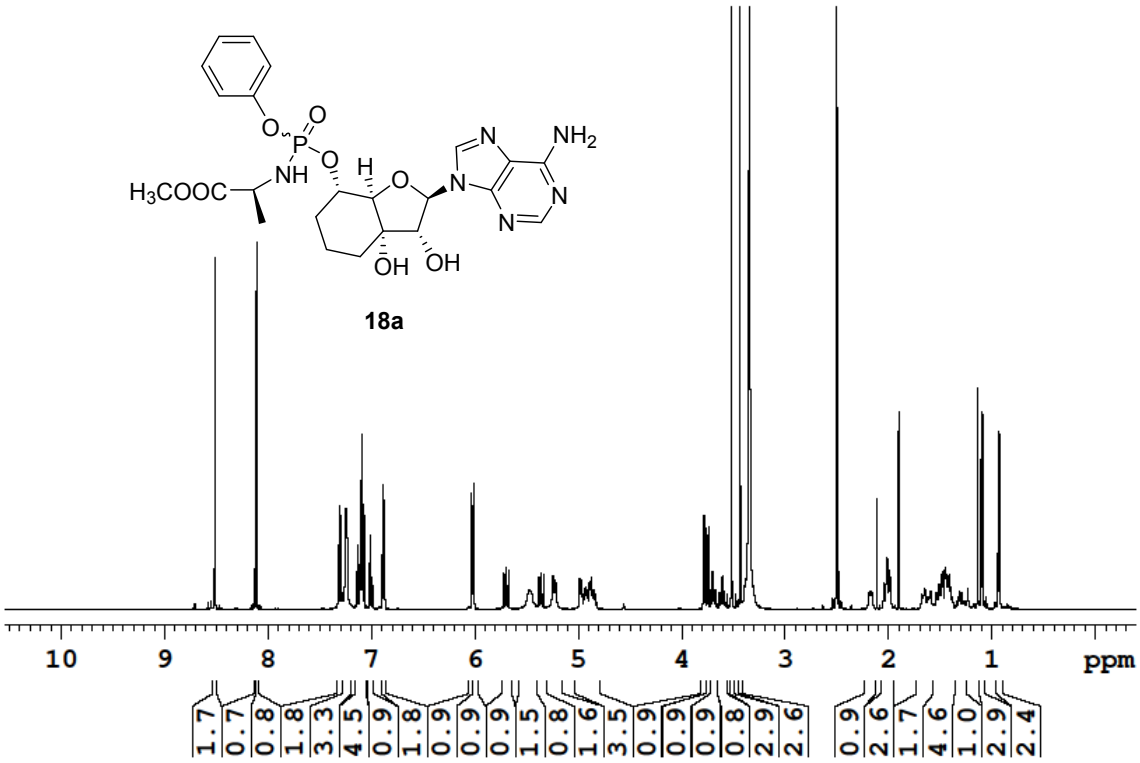

O
P
O
O
NH
H
O
N
N
NH2
H3COOC
N
N
OH
OH

17b

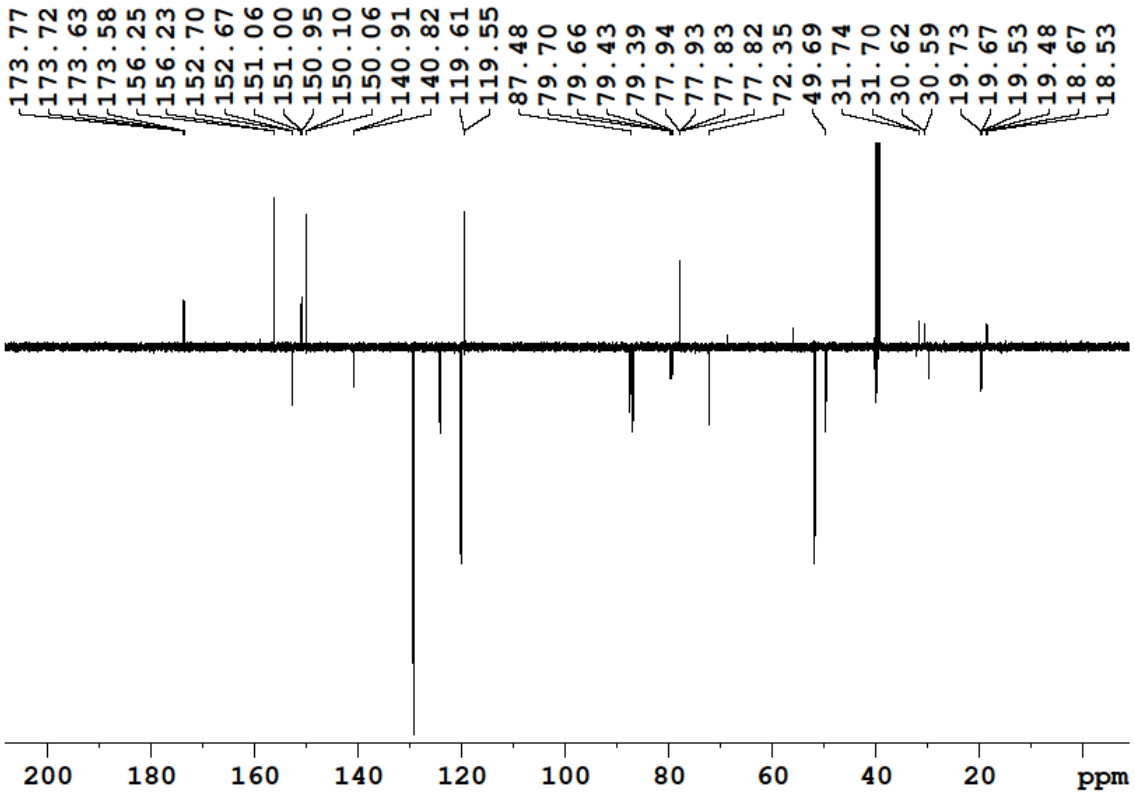

10 9 8 7 6 5 4 3 2 1 ppm
1.9 0.8 0.9 7.4 5.9 1.8 1.8 5.5 1.9 2.2 1.5 1.7 1.9 3.0 2.6 2.6 3.0

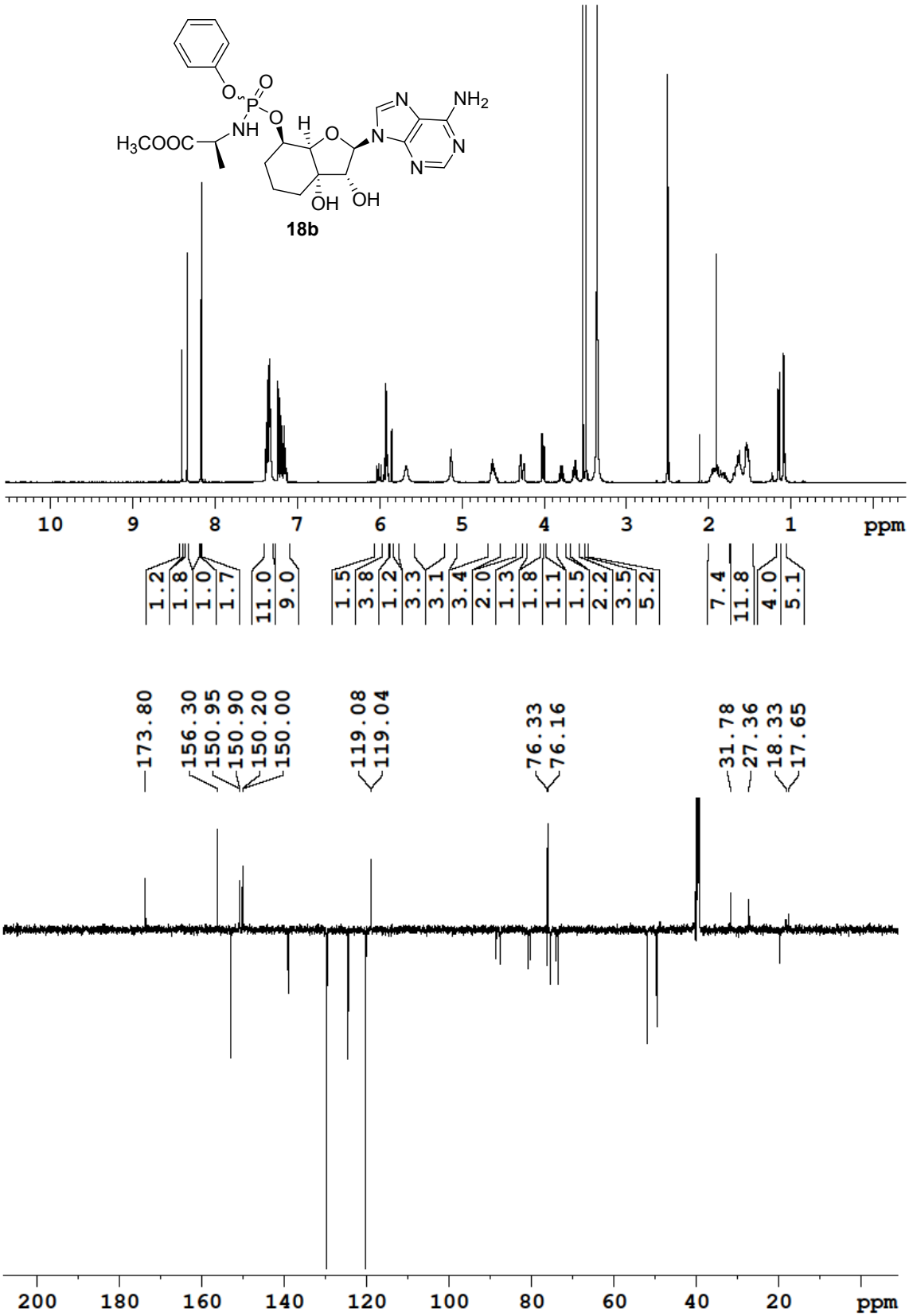

173.90
173.72
156.31
152.88
150.89
150.20
140.70
140.35
129.77
124.69
120.36
120.32
119.48
87.36
84.71
74.81
52.06
52.00
50.04
49.89
33.91
33.56
19.96
19.91
19.66
19.60
200 180 160 140 120 100 80 60 40 20 ppm


3.96
3.73
15
10
5
0
−5
−10
ppm


H3COOC
NH
O
P
O
O
H
O
N
N
N
N
NH2
OH
OH
10
9
8
7
6
5
4
3
2
1
ppm
1.7
0.7
0.8
1.8
3.3
4.5
0.9
1.8
0.9
0.9
0.9
1.5
0.8
1.6
3.5
0.9
0.9
0.9
0.8
2.9
2.6
0.9
2.6
1.7
4.6
1.0
2.9
2.4

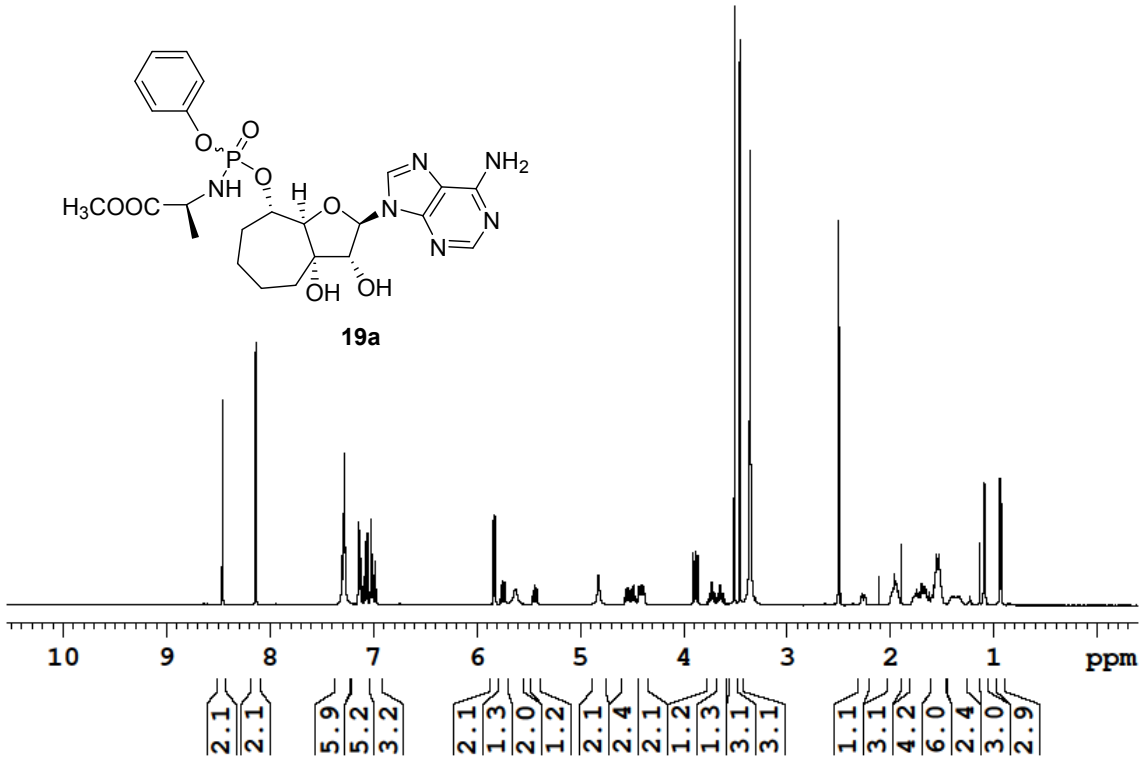
18a

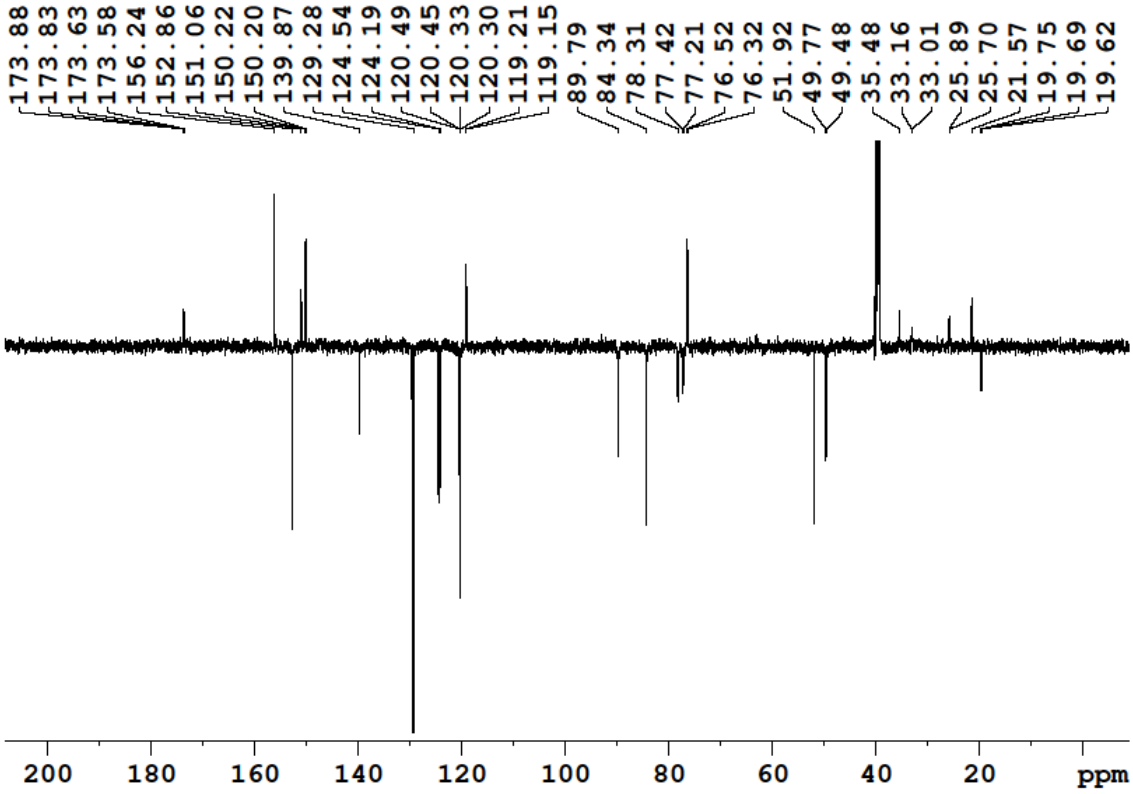

173.77
173.72
173.63
173.58
156.25
156.23
152.70
152.67
151.06
151.00
150.95
150.10
150.06
140.91
140.82
119.61
119.55
87.48
79.70
79.66
79.43
79.39
77.94
77.93
77.83
77.82
72.35
49.69
31.74
31.70
30.62
30.59
19.73
19.67
19.53
19.48
18.67
18.53
200
180
160
140
120
100
80
60
40
20
ppm


18b
10
9
8
7
6
5
4
3
2
1
ppm
1.2
1.8
1.0
1.7
11.0
9.0
1.5
3.8
1.2
3.3
3.1
3.4
2.0
1.3
1.8
1.1
1.5
2.2
3.5
5.2
7.4
11.8
4.0
5.1
173.80
156.30
150.95
150.90
150.20
150.00
119.08
119.04
76.33
76.16
31.78
27.36
18.33
17.65
200
180
160
140
120
100
80
60
40
20
ppm

O
O
P
O
NH
H
O
N
N
NH2
N
N
H3COOC
OH
OH

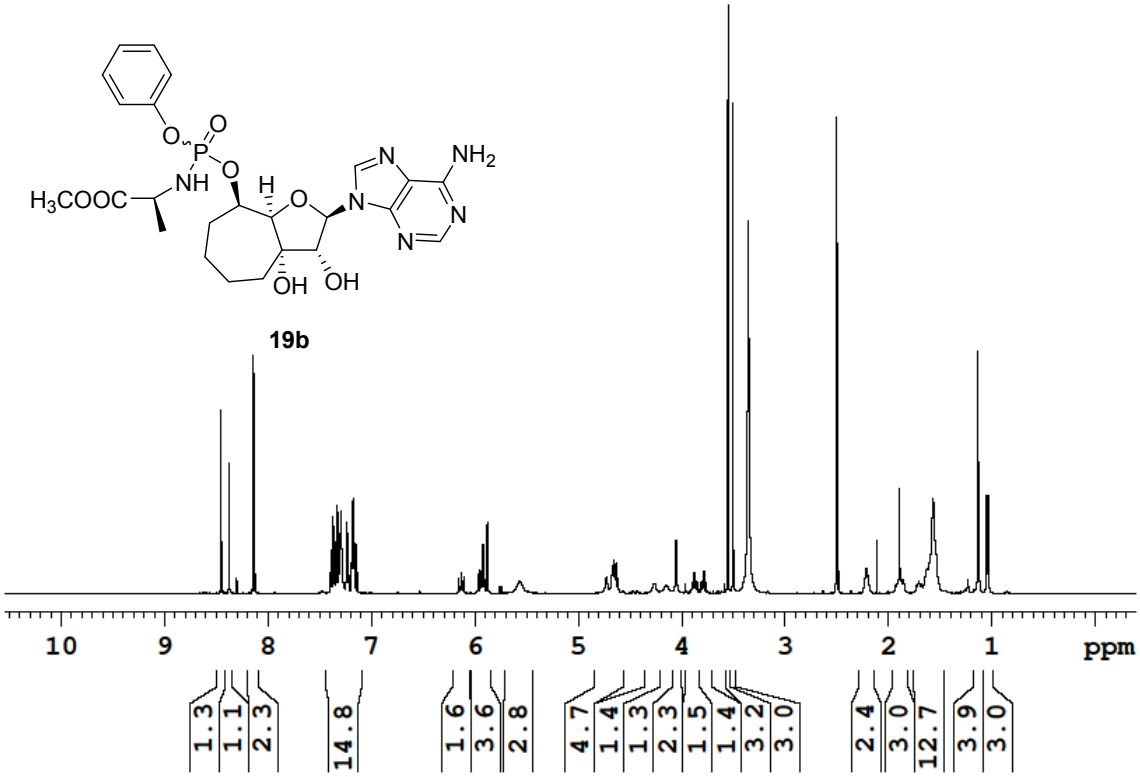
19a

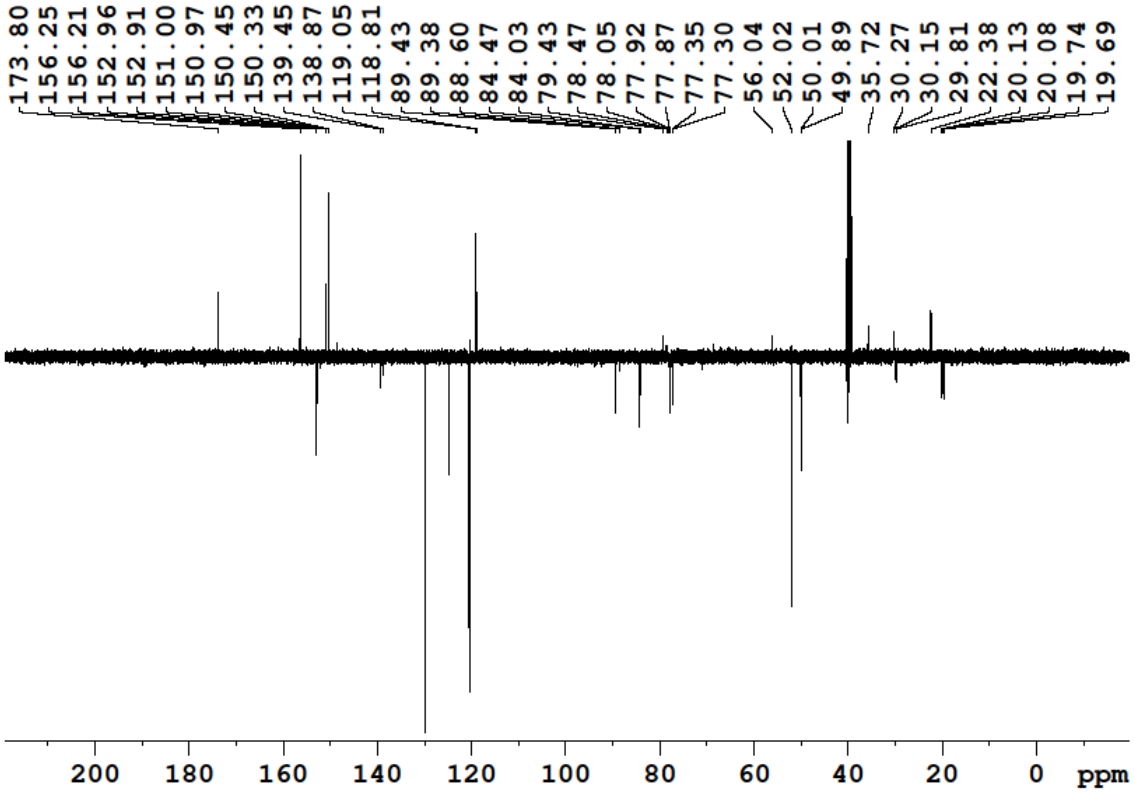

10
9
8
7
6
5
4
3
2
1
ppm
2.1
2.1
5.9
5.2
3.2
2.1
1.3
2.0
1.2
2.1
2.4
2.1
1.2
1.3
3.1
3.1
1.1
3.1
4.2
6.0
2.4
3.0
2.9

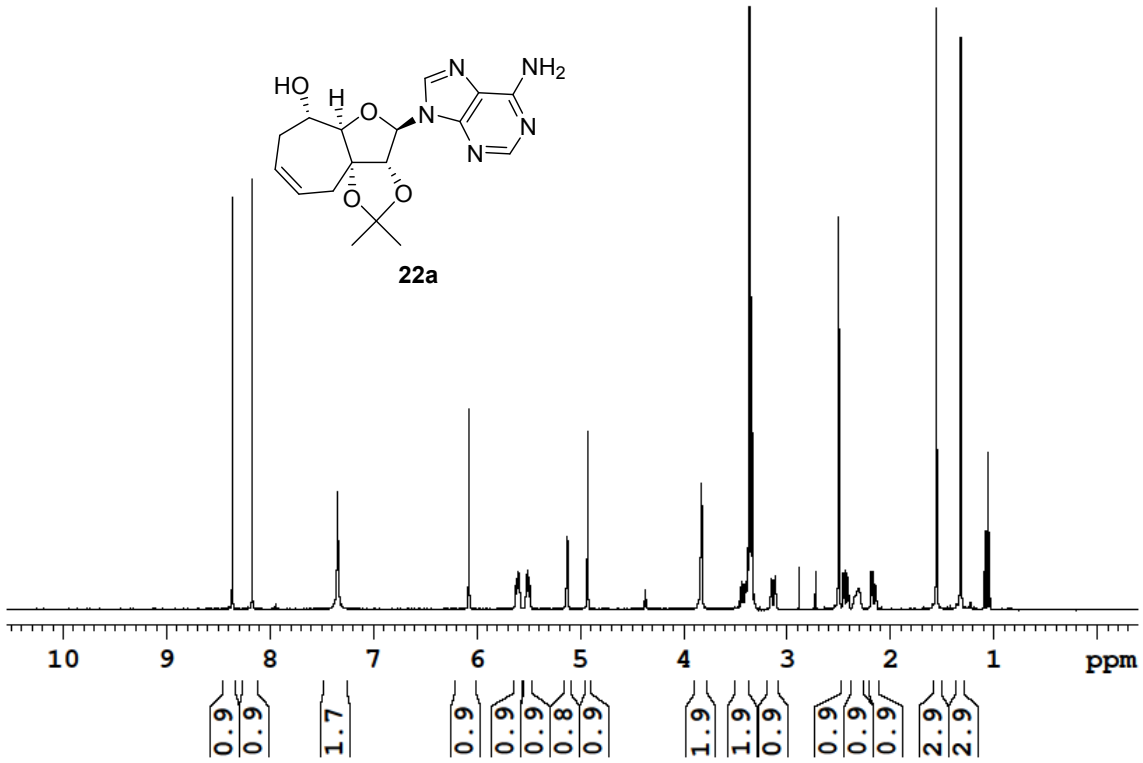

173.88
173.83
173.63
173.58
156.24
152.86
151.06
150.22
150.20
139.87
129.28
124.54
124.19
120.49
120.45
120.33
120.30
119.21
119.15
89.79
84.34
78.31
77.42
77.21
76.52
76.32
51.92
49.77
49.48
35.48
33.16
33.01
25.89
25.70
21.57
19.75
19.69
19.62
200
180
160
140
120
100
80
60
40
20
ppm

O
P
O
NH
H
O
N
N
N
NH2
H3COOC
OH
OH

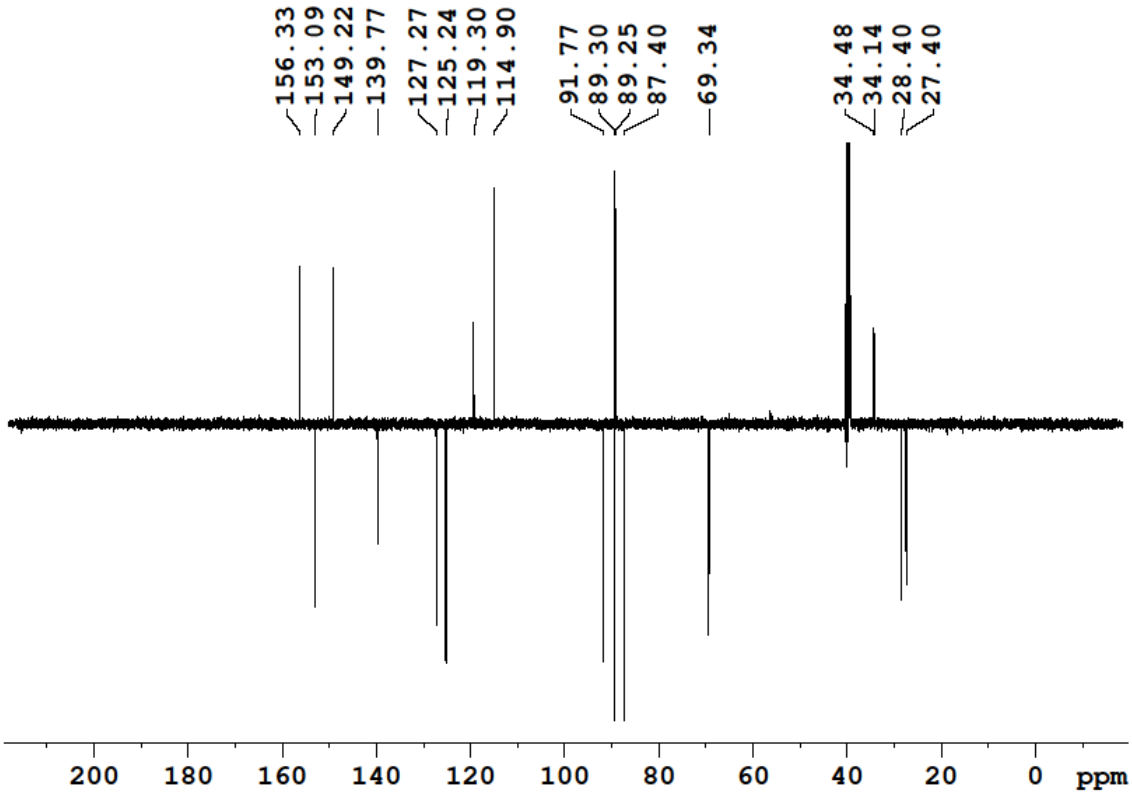
19b

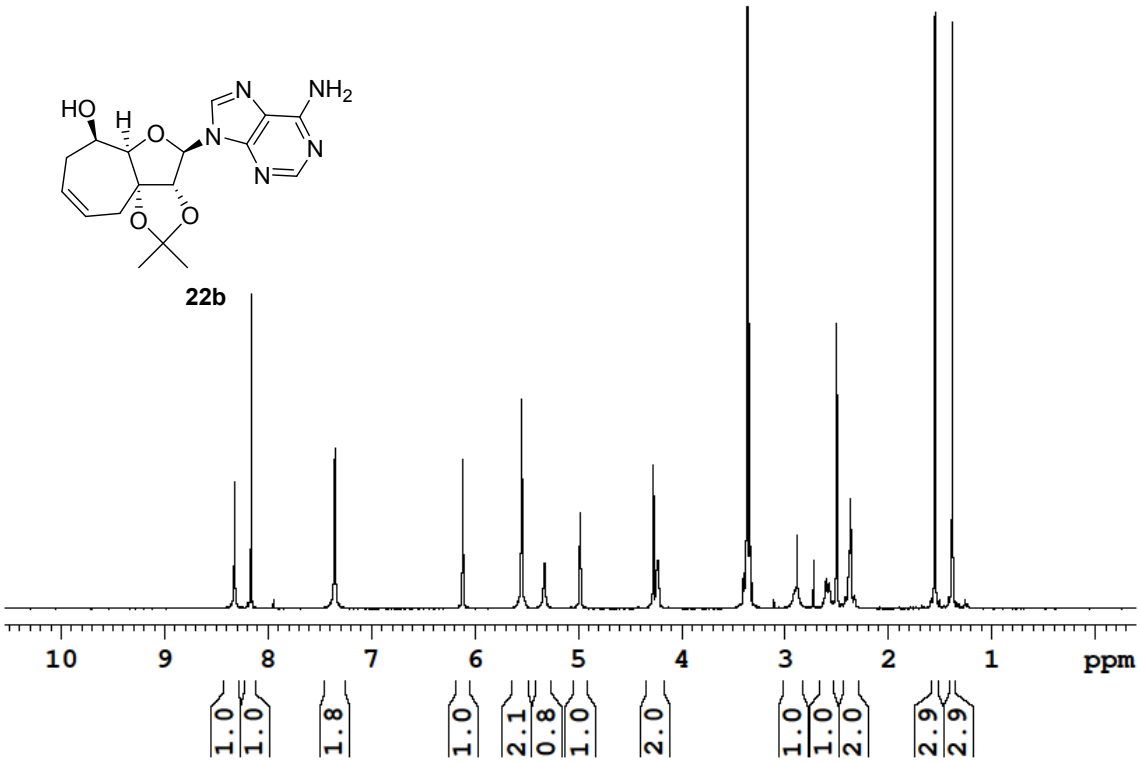

10
9
8
7
6
5
4
3
2
1
ppm
1.3
1.1
2.3
14.8
1.6
3.6
2.8
4.7
1.4
1.3
2.3
1.5
1.4
3.2
3.0
2.4
3.0
12.7
3.9
3.0


173.80
156.25
156.21
152.96
152.91
151.00
150.97
150.45
150.33
139.45
138.87
119.05
118.81
89.43
89.38
88.60
84.47
84.03
79.43
78.47
78.05
77.92
77.87
77.35
77.30
56.04
52.02
50.01
49.89
35.72
30.27
30.15
29.81
22.38
20.13
20.08
19.74
19.69
200
180
160
140
120
100
80
60
40
20
0
ppm

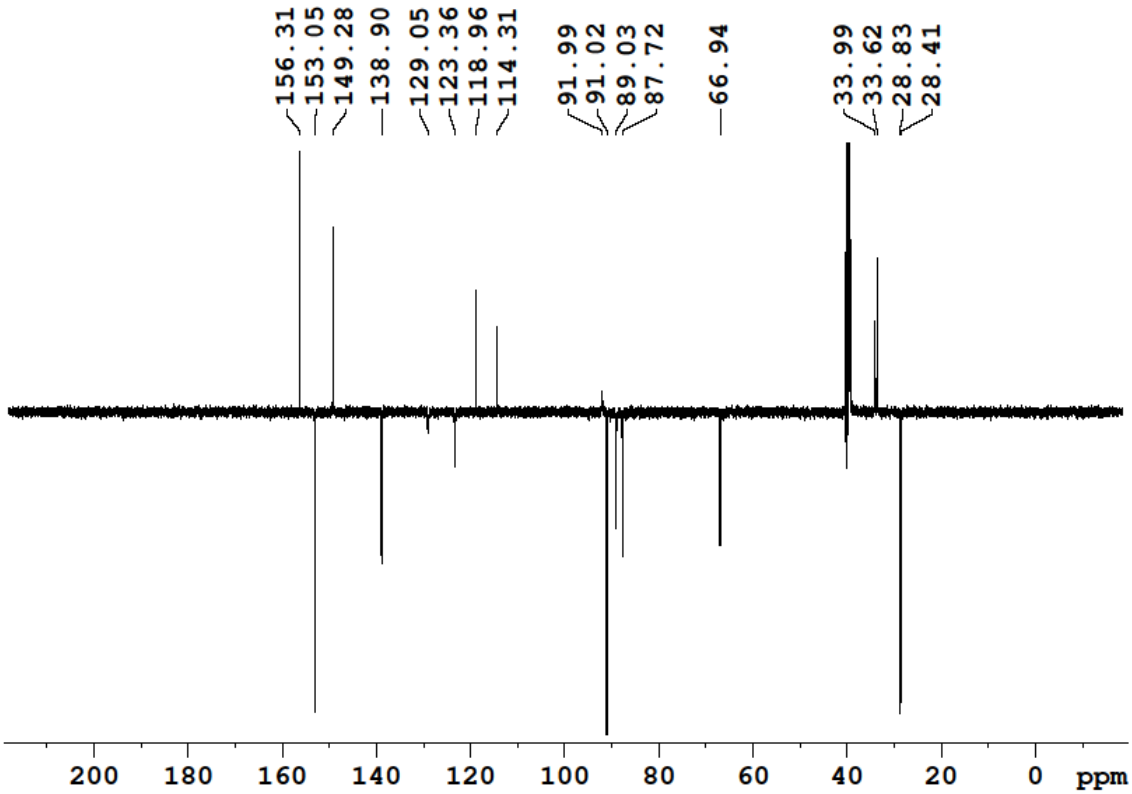

HO
H
O
N
N
N
N
NH2
O
O
10
9
8
7
6
5
4
3
2
1
ppm
0.9
0.9
1.7
0.9
0.9
0.9
0.8
0.9
1.9
1.9
0.9
0.9
0.9
0.9
2.9
2.9

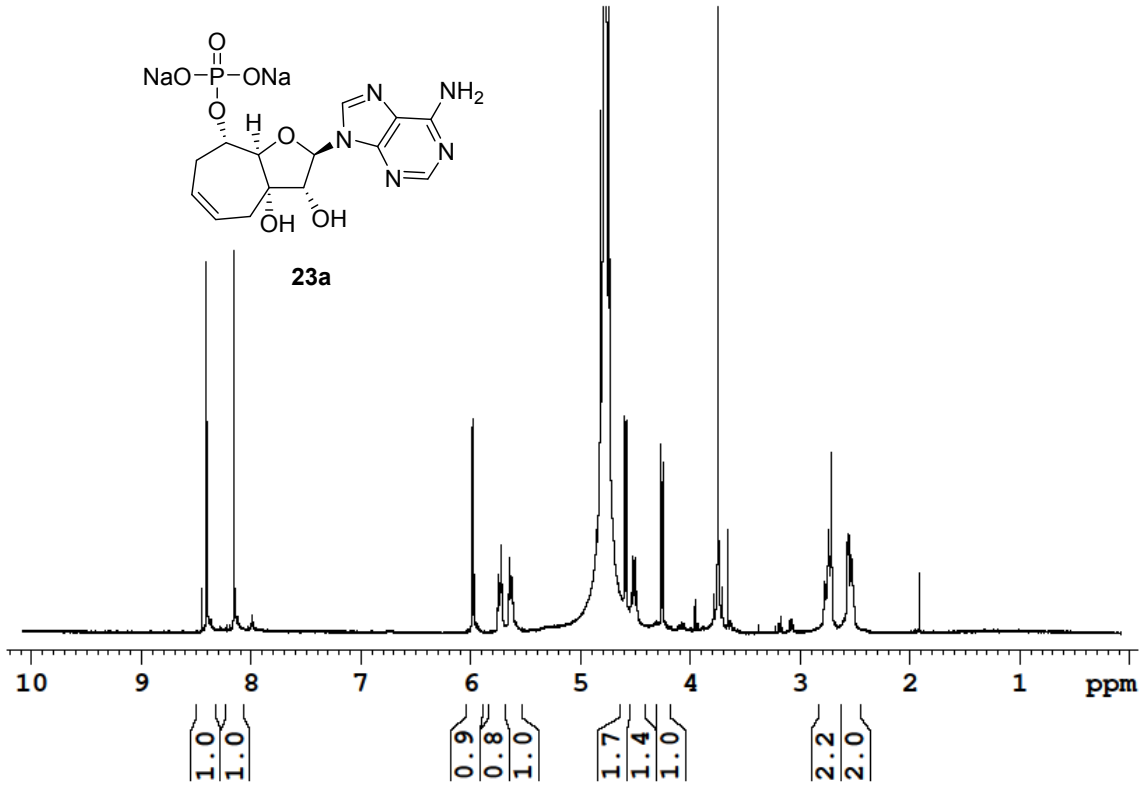
22a


156.33
153.09
149.22
139.77
127.27
125.24
119.30
114.90
91.77
89.30
89.25
87.40
69.34
34.48
34.14
28.40
27.40
200
180
160
140
120
100
80
60
40
20
0
ppm

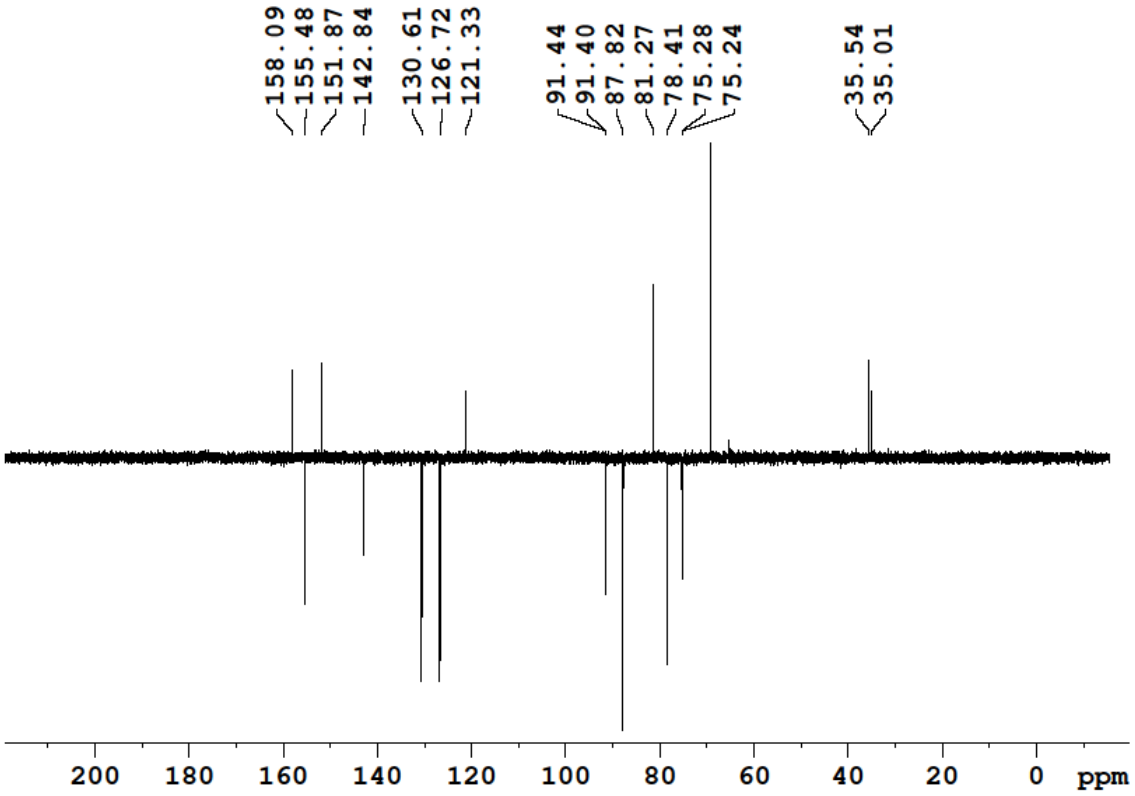

HO
H
O
N
N
N
N
NH2
O
O
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
1.8
1.0
2.1
0.8
1.0
2.0
1.0
1.0
2.0
2.9
2.9

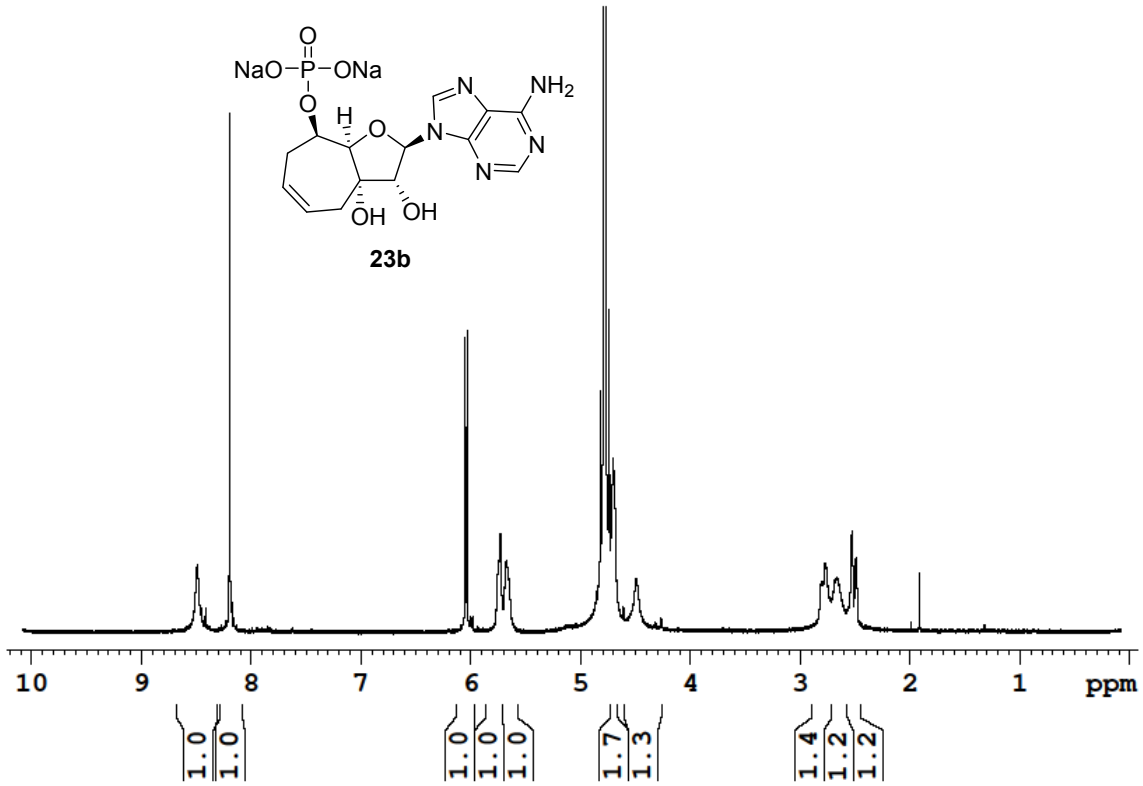
22b

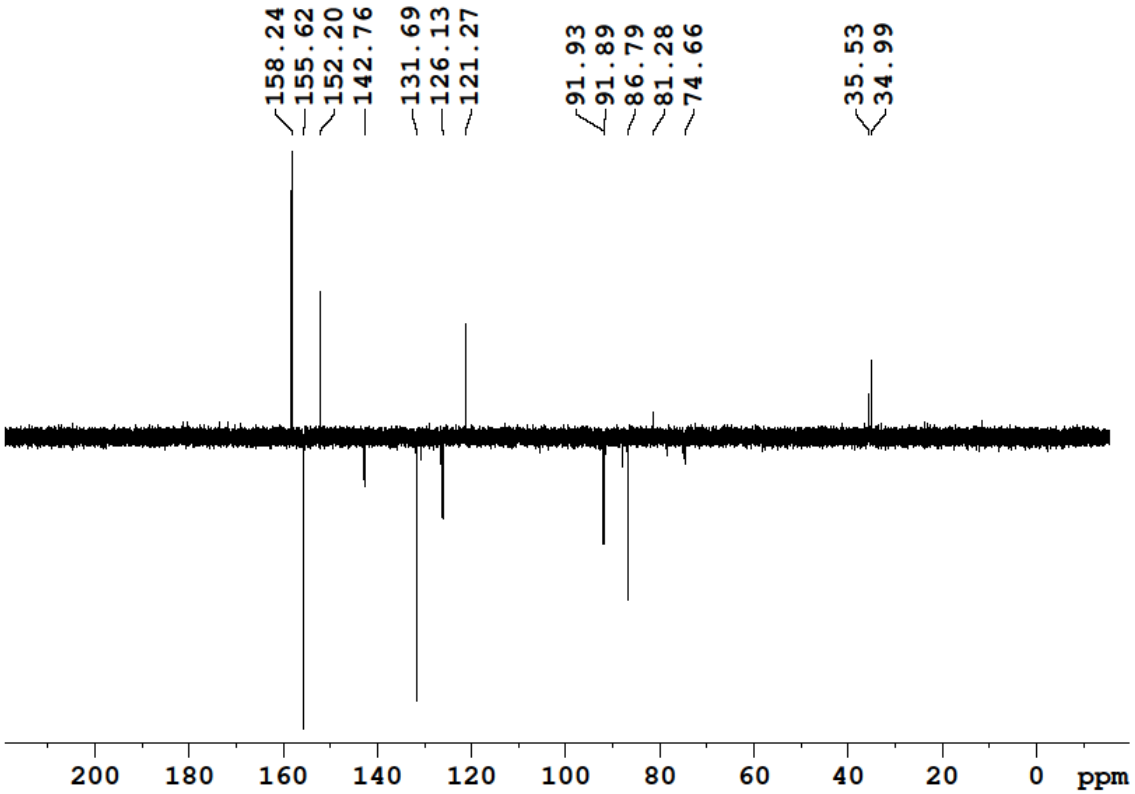

156.31
153.05
149.28
138.90
129.05
123.36
118.96
114.31
91.99
91.02
89.03
87.72
66.94
33.99
33.62
28.83
28.41
200
180
160
140
120
100
80
60
40
20
0
ppm


NaO
P
ONa
O
H
N
NH2
OH
OH
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
0.9
0.8
1.0
1.7
1.4
1.0
2.2
2.0

23a

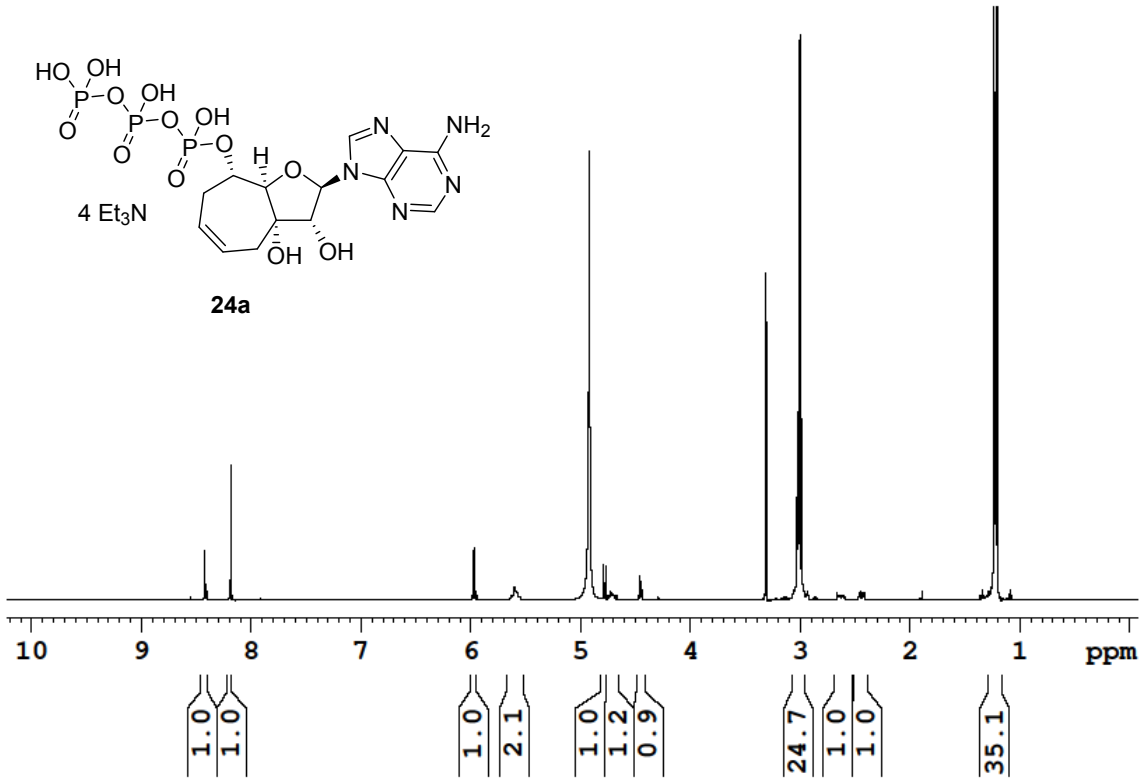

158.09
155.48
151.87
142.84
130.61
126.72
121.33
91.44
91.40
87.82
81.27
78.41
75.28
75.24
35.54
35.01
200
180
160
140
120
100
80
60
40
20
0
ppm

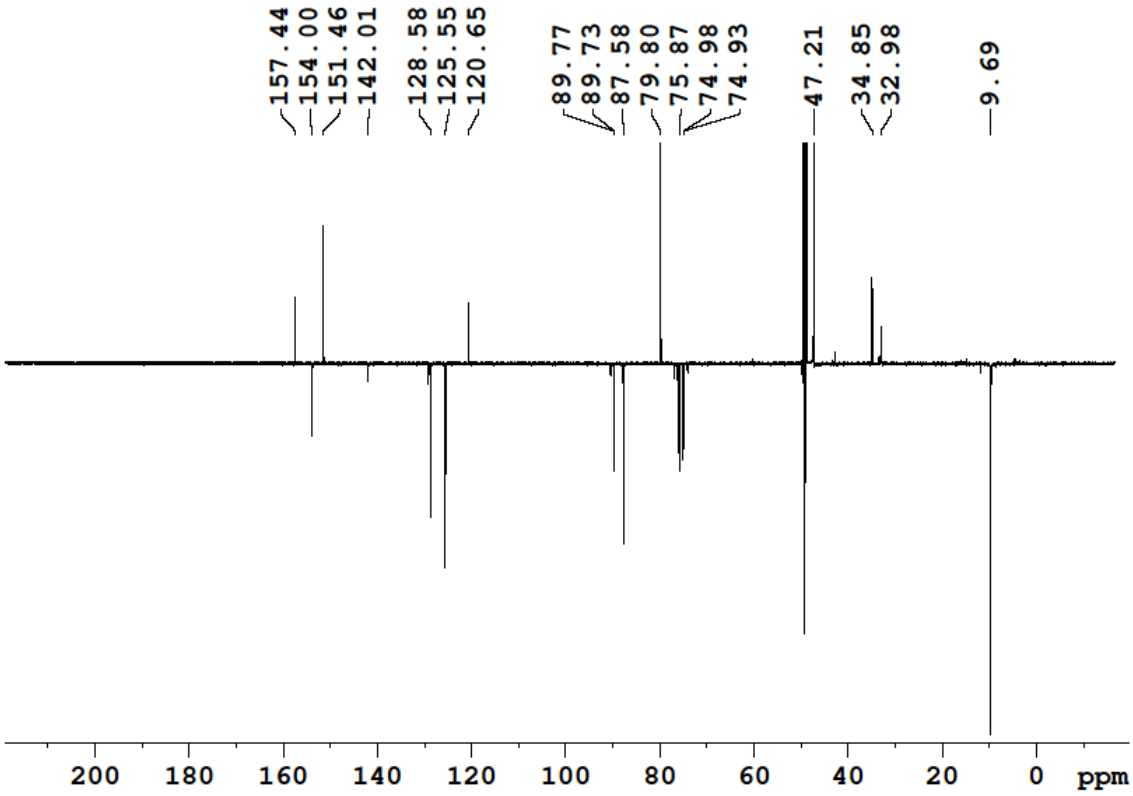

NaO−P−ONa
O
O
H
O
N
N
N
N
NH2
OH
OH
23b
10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
1.0
1.0
1.0
1.7
1.3
1.4
1.2
1.2

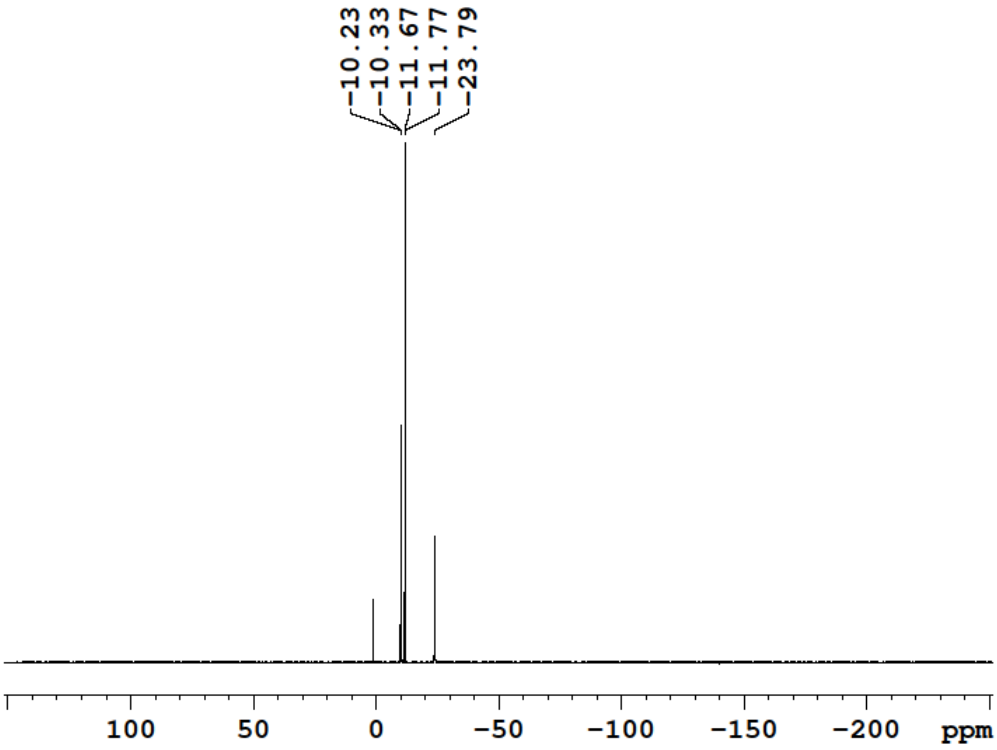

158.24
155.62
152.20
142.76
131.69
126.13
121.27
91.93
91.89
86.79
81.28
74.66
35.53
34.99
200
180
160
140
120
100
80
60
40
20
0
ppm

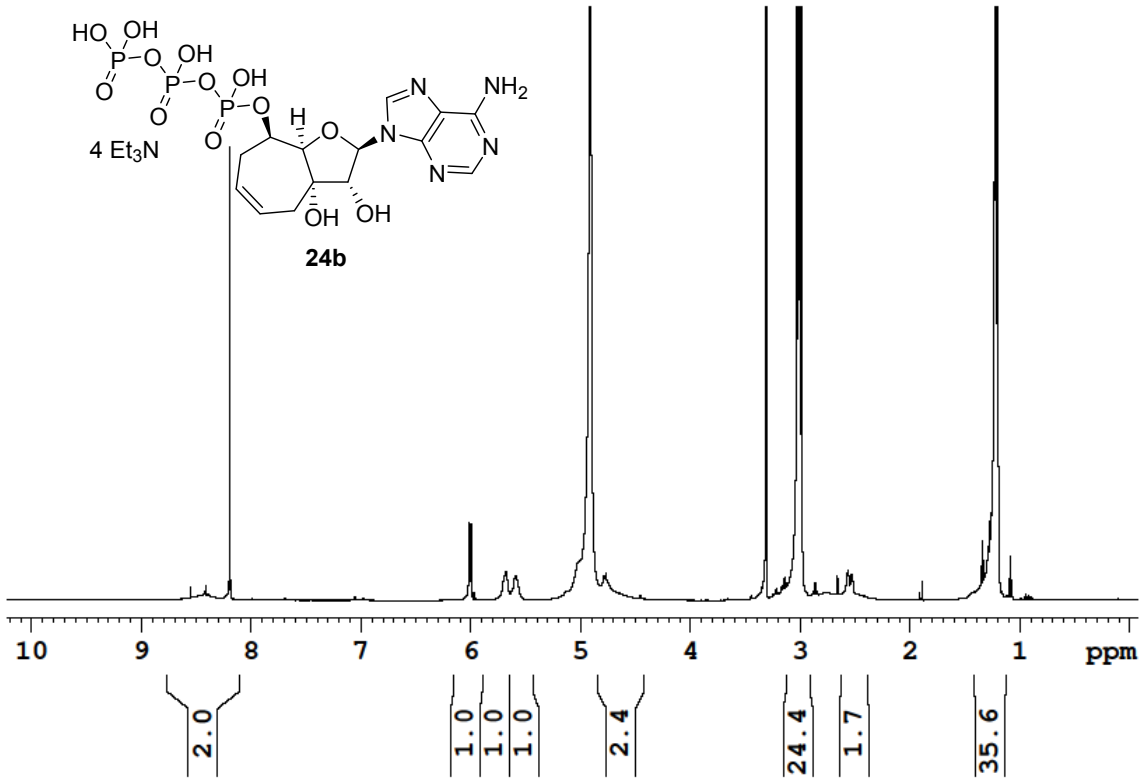
HO
OH
P
O
OH
P
O
OH
P
O
O
O
O
H
O
N
N
N
N
NH2
OH
OH
4 Et3N

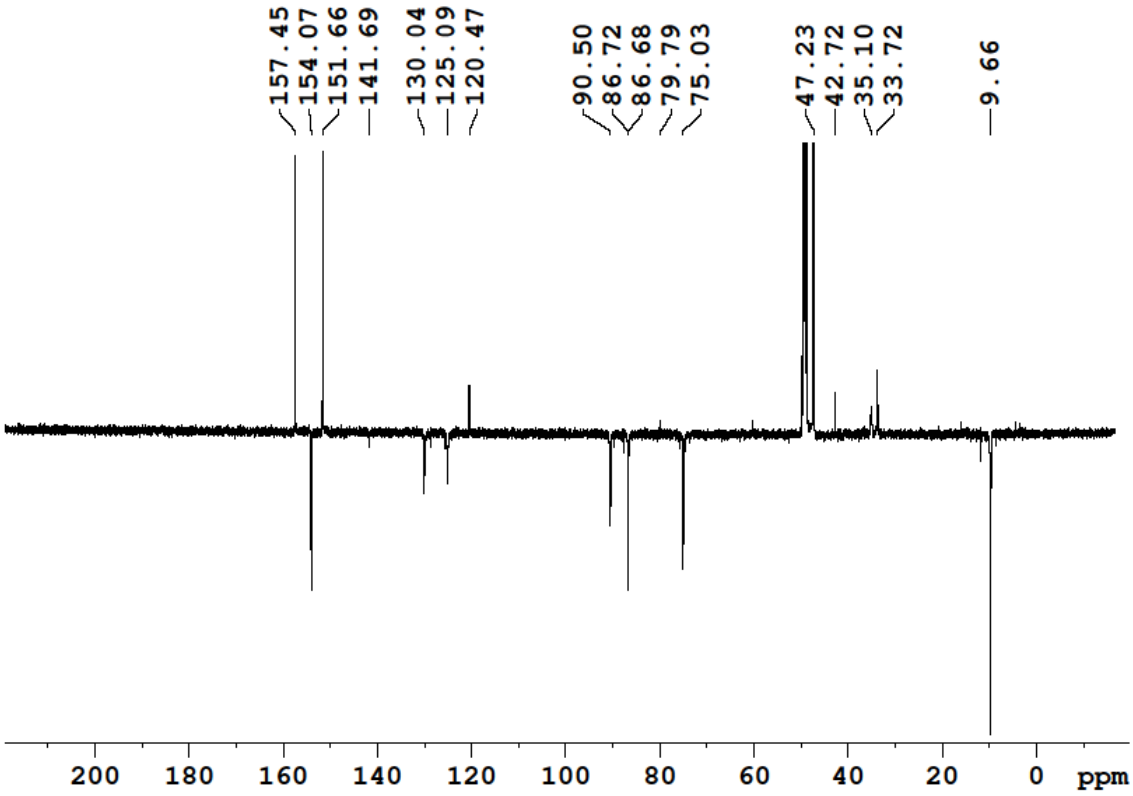
24a

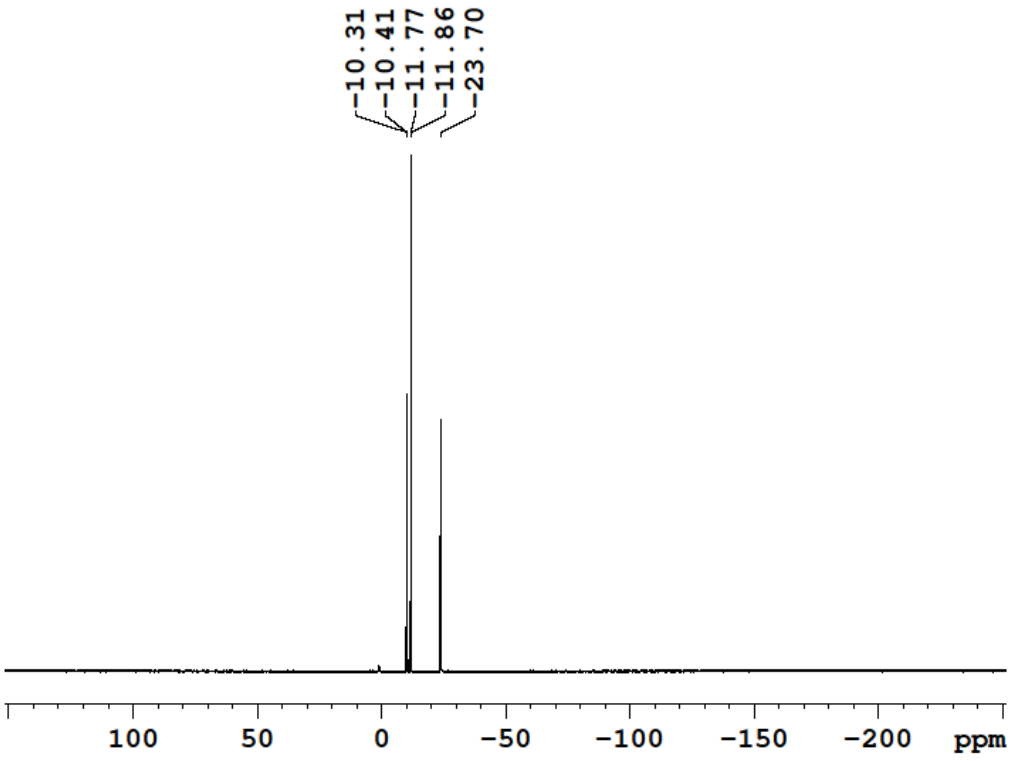

10
9
8
7
6
5
4
3
2
1
ppm
1.0
1.0
1.0
2.1
1.0
1.2
0.9
24.7
1.0
1.0
35.1


157.44
154.00
151.46
142.01
128.58
125.55
120.65
89.77
89.73
87.58
79.80
75.87
74.98
74.93
47.21
34.85
32.98
9.69
200
180
160
140
120
100
80
60
40
20
0
ppm


-10.23
-10.33
-11.67
-11.77
-23.79
100
50
0
-50
-100
-150
-200
ppm


4 Et3N
24b
10
9
8
7
6
5
4
3
2
1
ppm
2.0
1.0
1.0
1.0
2.4
24.4
1.7
35.6


157.45
154.07
151.66
141.69
130.04
125.09
120.47
90.50
86.72
86.68
79.79
75.03
47.23
42.72
35.10
33.72
9.66
200
180
160
140
120
100
80
60
40
20
0
ppm


-10.31
-10.41
-11.77
-11.86
-23.70
100
50
0
-50
-100
-150
-200
ppm